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(54) **Title:** SMALL *STREPTOCOCCUS PYOGENES* ANTIGENS AND THEIR USE

(57) **Abstract:** The present invention relates to a peptide consisting of one antigen of *Streptococcus pyogenes* (*S. pyogenes*) of any of the SEQ ID NOS: 1 to 7 or a functional active variant thereof, optionally further consisting of additional amino acid residue(s); a nucleic acid coding for the same; a pharmaceutical composition, especially a vaccine, comprising said peptide or said nucleic acid; an antibody or functional active fragment thereof specifically binding to the antigen; a hybridoma cell line which produces said antibody; a method for producing said antibody; a pharmaceutical composition comprising said antibody; the use of said peptide or said nucleic acid for the manufacture of a medicament for the immunization or treatment of a subject; the use of said antibody or functional fragment thereof for the manufacture of a medicament for the treatment of an infection; a method of diagnosing a *S. pyogenes* infection; a method for identifying a ligand capable of binding to said peptide; and the use of said peptide for the isolation and/or purification and/or identification of an interaction partner of the peptide.

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Small *Streptococcus pyogenes* Antigens and their Use

The present invention relates to a peptide consisting of one antigen of *Streptococcus pyogenes (S. pyogenes)* of any of the SEQ ID NOS: 1 to 7 or a functional active variant thereof, optionally further consisting of additional amino acid residue(s); a nucleic acid coding for the same; a pharmaceutical composition, especially a vaccine, comprising said peptide or said nucleic acid; an antibody or functional active fragment thereof specifically binding to the antigen; a hybridoma cell line which produces said antibody; a method for producing said antibody; a pharmaceutical composition comprising said antibody; the use of said peptide or said nucleic acid for the manufacture of a medicament for the immunization or treatment of a subject; the use of said antibody or functional fragment thereof for the manufacture of a medicament for the treatment of an infection; a method of diagnosing a *S. pyogenes* infection; a method for identifying a ligand capable of binding to said peptide; and the use of said peptide for the isolation and/or purification and/or identification of an interaction partner of the peptide.

Streptococcus pyogenes, also called group A streptococcus (GAS), is an important gram-positive extracellular bacterial pathogen and commonly infects humans. GAS colonizes the throat or skin and is responsible for a number of suppurative infections and non-suppurative sequelae. It is primarily a disease of children and causes a variety of infections including bacterial pharyngitis, scarlet fever, impetigo and sepsis in humans. Decades of epidemiological studies have led to the concept of distinct throat and skin strains, where certain serotypes are often associated with throat or skin infections, respectively (Cunningham, M. (2000). Clin Microbiol Rev **13**: 470-511). GAS has been discovered responsible for streptococcal toxic shock syndrome associated necrotizing fasciitis which is recently resurgent in the USA (Cone, L., et al. (1987). New Engl J Med **317**: 146-9; Stevens, D. (1992). Clin Infect Dis **14**: 2-11) and has been described as the "flesh eating" bacterium which invades skin and soft tissues leading to tissue or limb destruction.

Several post-streptococcal sequelae may occur in humans subsequent to infection, such as acute rheumatic fever, acute glomerulonephritis and reactive arthritis. Acute rheumatic

fever and rheumatic heart disease are of these the most serious autoimmune sequelae and have led to disability and death of children worldwide. *S. pyogenes* can also causes severe acute diseases such as scarlet fever and necrotizing fasciitis and has been associated with Tourette's syndrome, tics and movement and attention disorders.

Group A streptococci are the most common bacterial cause of sore throat and pharyngitis and account for at least 16% of all office calls in a general medical practice, season dependent (Hope-Simpson, R. (1981). J Hyg (Lond) **87**: 109-29). It primarily affects children in school-age between 5 to 15 years of age (Cunningham, supra). All ages are susceptible to spread of the organism under crowded conditions, for example in schools. GAS are not considered normal flora though, but pharyngeal carriage of group A streptococci can occur without clinical symptoms.

Group A streptococci can be distinguished by the Lancefield classification scheme of serologic typing based on their carbohydrate or classified into M protein serotypes based on a surface protein that can be extracted by boiling bacteria with hydrochloric acid. This has led to the identification of more than 80 serotypes, which can also be typed by a molecular approach (emm genes). Molecular typing has identified more than 150 individual emm types. Certain M protein serotypes of *S. pyogenes* are mainly associated with pharyngitis and rheumatic fever, while others mainly seem to cause pyoderma and acute glomerulonephritis (Cunningham, supra).

Also implicated in causing pharyngitis and occasionally toxic shock are group C and G streptococci, which must be distinguished after throat culture (Hope-Simpson, supra; Bisno, A., et al. (1987). Infect Immun **55**: 753-7).

Currently, streptococcal infections can only be treated by antibiotic therapy. However, 25-30% of those treated with antibiotics show recurrent disease and/or shed the organism in mucosal secretions. There is at present no preventive treatment (vaccine) available to avoid streptococcal infections.

Thus, there remains a need for an effective treatment to prevent or ameliorate streptococcal infections. A vaccine could not only prevent infections by streptococci, but more

specifically prevent or ameliorate colonization of host tissues, thereby reducing the incidence of pharyngitis and other suppurative infections. Elimination of non-suppurative sequelae such as rheumatic fever, acute glomerulonephritis, sepsis, toxic shock and necrotizing fasciitis would be a direct consequence of reducing the incidence of acute infection and carriage of the organism. Vaccines capable of showing cross-protection against other streptococci would also be useful to prevent or ameliorate infections caused by all other beta-hemolytic streptococcal species, namely groups A, B, C and G.

A vaccine can contain a whole variety of different antigens. Examples of antigens are whole-killed or attenuated organisms, subfractions of these organisms/tissues, proteins, or, in their most simple form, peptides. Antigens can also be recognized by the immune system in form of glycosylated proteins or peptides and may also be or contain polysaccharides or lipids. Short peptides can be used since for example cytotoxic T-cells (CTL) recognize antigens in form of short usually 8-11 amino acids long peptides in conjunction with major histocompatibility complex (MHC). B-cells can recognize linear epitopes as short as 4-5 amino acids, as well as three-dimensional structures (conformational epitopes).

In some circumstances, adjuvants may be useful for sustaining antigen-specific immune responses. Primarily, adjuvants are acting, but are not restricted in their mode of action, on so-called antigen presenting cells (APCs). These cells usually first encounter the antigen(s) followed by presentation of processed or unmodified antigen to immune effector cells. Intermediate cell types may also be involved. Only effector cells with the appropriate specificity are activated in a productive immune response. The adjuvant may also locally retain antigens and co-injected other factors. In addition the adjuvant may act as a chemoattractant for other immune cells or may act locally and/or systemically as a stimulating agent for the immune system.

Approaches to develop a group A streptococcal vaccine have focused mainly on the cell surface M protein of *S. pyogenes* (Bessen, D., et al. (1988). Infect Immun **56**: 2666-2672; Bronze, M., et al. (1988). J Immunol **141**: 2767-2770). Since more than 80 different M serotypes of *S. pyogenes* exist and new serotypes continually arise (Fischetti, V. (1989). Clin Microbiol Rev **2**: 285-314), inoculation with a limited number of serotype-specific M

protein or M protein derived peptides will not likely be effective in protecting against all other M serotypes. Furthermore, it has been shown that the conserved region of the M protein contains an amino acid sequence, which is immunologically cross-reactive with human heart tissue, which is thought to account for heart valve damage associated with rheumatic fever (Fenderson, P., et al. (1989). J Immunol **142**: 2475-2481).

There are other proteins under consideration for vaccine development, such as the erythrogenic toxins, streptococcal pyrogenic exotoxin A and streptococcal pyrogenic exotoxin B (Lee, P. K. (1989). J Clin Microbiol **27**: 1890-2). Immunity to these toxins could possibly prevent the deadly symptoms of streptococcal toxic shock, but it may not prevent colonization by group A streptococci.

The use of the above described proteins as antigens for a potential vaccine as well as a number of additional candidates (Ji, Y., et al. (1997). Infect Immun **65**: 2080-2087; Guzman, C., et al. (1999). J Infect Dis **179**: 901-6) resulted mainly from a selection based on easiness of identification or chance of availability. There is a demand to identify efficient and relevant antigens for *S. pyogenes*.

WO 2004/078907 describes a method for identification, isolation and production of hyperimmune serum reactive antigens from *Streptococcus pyogenes*.

The antigens described herein focus on regions shown in the present application to be protective. A suitable antigen size to obtain protection varies based on different factors such as the type of protective epitope (e.g., conformational versus linear) and the number of protective epitopes providing a level of protection. Large antigens containing regions not providing useful protection may be disadvantageous in the context of immunization. First, providing of smaller antigens eases production of the protein in recombinant form. It is generally accepted that it is more difficult to produce larger proteins. Smaller proteins may be produced in a more economic manner, thus saving costs, particularly in the health care system. Second, reducing the size of antigenic proteins used for vaccination may lead to safer products. Eliminating extra sequences in antigenic proteins is desirable, since this reduces the probability of inducing antibodies which can cause cross-reactions with human tissues. Third, proteins used for vaccination may contain more than one antigen, the

antigens directed either against the same disease or against different diseases, in order to obtain a more effective vaccination or vaccination against several diseases. However, if the single antigens are too large a combination into one protein is not feasible.

Accordingly, one problem underlying the present invention was to provide alternative means for the development of medicaments such as vaccines against *S. pyogenes* infection, particularly smaller proteins.

Surprisingly, the object has been solved by a peptide consisting of one antigen of *S. pyogenes* of the SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7 or a functional active variant of one antigen of *S. pyogenes* of the SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7. These peptides are referred to as antigenic peptides.

The sequences of SEQ ID NOS: 1 to 7 are characterized in table 1 of the present specification. The underlying amino acid sequences are disclosed in the attached sequence data. The peptides of SEQ ID NOS: 1 to 7 have been shown to induce an immune response and/or to show protection against *S. pyogenes* in a sepsis and/or lethality model (see Example 1). Functional active variants are obtained by changing the sequence of the antigen as defined below and are characterized by having a biological activity similar to that displayed by the antigen of any of the sequences of SEQ ID NO: 1 to 7 from which it is derived, including the ability to induce immune responses and/or to show protection against *S. pyogenes* e.g. in a sepsis and/or lethality model.

In some embodiments of the invention the peptide of the invention consists of one antigen of *S. pyogenes* of the SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7 or a functional active variant of one antigen of *S. pyogenes* of the SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7; and

a) 1 to 350 additional amino acid residue(s), preferably 1 to 200, more preferably 1 to 150, even more preferably at most 1 to 100, still more preferably at most 1 to 50,

most preferably 1, 2, 3, 4, 5, 10, 15, 20 or 25 additional amino acids residue(s) if the antigen is SEQ ID NO: 1; or

b) 1 to 200 additional amino acid residue(s), preferably 1 to 150, more preferably 1 to 100, even more preferably at most 1 to 50, still more preferably at most 1 to 25, most preferably 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 additional amino acids residue(s) if the antigen is SEQ ID NO: 2; or

c) 1 to 100 additional amino acid residue(s), preferably 1 to 75, more preferably 1 to 50, even more preferably at most 1 to 25, still more preferably at most 1 to 10, most preferably 1, 2, 3, 4 or 5 additional amino acids residue(s) if the antigen is that of SEQ ID NO: 3; or

d) 1 to 150 additional amino acid residue(s), preferably 1 to 100, more preferably 1 to 75, even more preferably at most 1 to 50, still more preferably at most 1 to 25, most preferably 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 additional amino acids residue(s) if the antigen is that of SEQ ID NO: 4; or

e) 1 to 450 additional amino acid residue(s), preferably 1 to 300, more preferably 1 to 150, even more preferably at most 1 to 100, still more preferably at most 1 to 50, most preferably 1, 2, 3, 4, 5, 10, 20, 30 or 40 additional amino acids residue(s) if the antigen is SEQ ID NO: 5; or

f) 1 to 250 additional amino acid residue(s), preferably 1 to 200, more preferably 1 to 150, even more preferably at most 1 to 100, still more preferably at most 1 to 50, most preferably 1, 2, 3, 4, 5, 10, 15, 20 or 25 additional amino acids residue(s) if the antigen is SEQ ID NO: 6 or SEQ ID NO: 7.

The antigen of *S. pyogenes* can be any of the antigens as defined above, namely as defined in any of the SEQ ID NOS: 1, 2, 3, 4, 5, 6 or 7, or a functional active variant thereof, wherein the functional active variant is as defined below.

The antigen or the functional active variant thereof may have added at least one additional amino acid residue heterologous or homologous to the peptide. Homologous refers to any amino acid or amino acid sequence which is identical to the amino acid sequence of the *S. pyogenes* protein from which the antigen is derived, wherein the sequences of SEQ ID NO: 1 to 7 are derived from the following proteins:

Sequence	derived from protein (as disclosed in e.g. WO 2004/078907 or in the attached sequence data)
SEQ ID NO: 1	Spy0269
SEQ ID NO: 2	Spy0292
SEQ ID NO: 3	Spy0292
SEQ ID NO: 4	Spy0416
SEQ ID NO: 5	Spy0416
SEQ ID NO: 6	Spy0416
SEQ ID NO: 7	Spy0872

In one embodiment the antigen or the functional active variant thereof having one or more additional amino acid residues (see above, particularly as defined in items (a) to (f)) further encompasses at least one amino acid residue heterologous to the antigen. The feature "heterologous amino acid" or "amino acid heterologous to the antigen or protein" refers to any amino acid which is different from that amino acid located adjacent to the antigen or protein in any naturally occurring protein of *S. pyogenes*, particularly from that of *S. pyogenes* SF370 (serotype M1). Therefore, the protein of the invention encompassing at least one heterologous amino acid refers to a protein which is different from any naturally occurring protein of *S. pyogenes* or fragment thereof, particularly which is different from that of *S. pyogenes* SF370 (serotype M1). The proteins from which the antigens of the invention are derived as well as a reference for their sequences are listed above.

In certain embodiments, the peptide consists of the antigen, optionally the at least one additional amino acid residue as defined above, and at least one additional heterologous amino acid sequence comprising a marker protein.

The additional sequence or amino acid residue(s) as defined above consists of (an) amino acid residue(s), which may be any amino acid, which may be either an L-and/or a D-amino acid, naturally occurring and otherwise. Preferably the amino acid is any naturally occurring amino acid such as alanine, cysteine, aspartic acid, glutamic acid, phenylalanine, glycine, histidine, isoleucine, lysine, leucine, methionine, asparagine, proline, glutamine, arginine, serine, threonine, valine, tryptophan or tyrosine.

However, the amino acid residue(s) may also be (a) modified or unusual amino acid(s). Examples of those are 2-aminoadipic acid, 3-aminoadipic acid, beta-alanine, 2-aminobutyric acid, 4-aminobutyric acid, 6-aminocaproic acid, 2-aminoheptanoic acid, 2-aminoisobutyric acid, 3-aminoisobutyric acid, 2-aminopimelic acid, 2,4-diaminobutyric acid, desmosine, 2,2'-diaminopimelic acid, 2,3-diaminopropionic acid, N-ethylglycine, N-ethylasparagine, hydroxylysine, allo-hydroxylysine, 3-hydroxyproloine, 4-hydroxyproloine, isodesmosine, allo-isoleucine, N-methylglycine, N-methylisoleucine, 6-N-Methyllysine, N-methylvaline, norvaline, norleucine or ornithine.

Additionally, the amino acid(s) may be subject to modifications such as posttranslational modifications. Examples of modifications include acetylation, amidation, blocking, formylation, γ-carboxyglutamic acid hydroxylation, glycosilation, methylation, phosphorylation and sulfatation.

If more than one additional or heterologous amino acid residue is present in the peptide, the amino acid residues may be the same or different from one another.

The antigenic peptide may be flanked by the amino acid residue(s) C-terminally, N-terminally, or C- and N-terminally.

In a further embodiment the peptide is as described above in the different embodiments, and contains a region that is essentially identical to any of the antigens of the SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7, but differs from the antigens of any of the of the SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7, in that is it derived from a homologous sequence of a different serotype of *S. pyogenes*, particularly wherein the serotype is M2, M3, M4, M5, M6, M11, M12, M14, M19, M22, M24, M25, M28, M44, M49, M57, M59, M60, M61, M76, M83, M84, M87, M89 or M118, especially *S. pyogenes* SF370.

Accordingly, the present invention also relates to antigens of different *S. pyogenes* isolates. Such homologues may easily be identified and isolated based on the nucleic acid and amino acid sequences disclosed herein. A homologous antigen of a different serotype may

be identified by e.g. sequence alignment. The homologous antigen sequence may vary from the antigen of any of the sequences of SEQ ID NO: 1 to 7 by one or more amino acid substitutions, deletions and/or additions. Preferably the homologous antigen sequence has the sequence of any of the homologous variants identified in the attached listing of amino acid sequences.

Examples of homologous sequences of a different serotype are detailed in the attached sequence data. Particularly, sequences homologous to the respective peptide of the invention are those listed below:

Full length amino acid sequence (SEQ ID NO)	**Peptide of the invention (SEQ ID NO)**	**Homologous amino acid sequences (SEQ ID NOS)**
57	1	58 to 67
68	2	69 to78
68	3	79 to 88
89	4	90 to 99
89	5	100 to 109
89	6	110 to 119
120	7	121 to 130

There are more than 150 emm types distinguished to date and the typing is based on the variable region at the 5' end of the emm gene (see e.g. Vitali, L., et al. (2002) J. Clin. Microbiol **40**: 679-681). The presence of a homologous antigen can accordingly be determined for every emm type. In addition it is possible to determine the variability of a particular antigen in the various emm types as described for the *sic* gene (Hoe N., et al. (2001) J. Inf. Dis. **183**: 633-9). The influence of the various M serotypes on the kind of disease it causes is summarized in a recent review (Cunningham, supra). In particular, two groups of serotypes can be distinguished:

1) Those causing Pharyngitis and Scarlet fever (e.g. M types 1, 3, 5, 6, 14, 18, 19, 24)
2) Those causing Pyoderma and Streptococcal skin infections (e.g. M types 2, 49, 57, 59, 60, 61)

This can serve as the basis to identify the relevance of an antigen for the use as a vaccine or in general as a drug targeting a specific disease.

The information e.g. from the homepage of the Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/ncidod/biotech/strep/emmtypes.htm) gives a dendrogram showing the relatedness of various emm types. Further relevant references are Vitali et al., supra (molecular emm typing method), Enright et al., Infection and Immunity 69: 2416-2427. (2001) (alternative molecular typing method (MLST)), Hoe et al., supra (example for the variation of one antigen (*sic*) in many different serotypes) and Cunningham, supra (review on GAS pathogenesis). All emm types are completely listed and are available at publicly available databases (e.g., through the CDC).

In another embodiment of the present invention the variant is a fragment. The fragment is characterized by being derived from the antigen as defined above by one or more amino acid deletions. The deletion(s) may be C-terminally, N-terminally and/or internally. Preferably the fragment is obtained by at most 10, 20, 30, 40, 50, 60, 80, 100, 150 or 200, more preferably by at most 10, 20, 30, 40 or 50, even more preferably at most 5, 10 or 15, still more preferably at most 5 or 10, most preferably 1, 2, 3, 4 or 5 amino acid deletion(s). The functional active fragment of the invention is characterized by having a biological activity similar to that displayed by the complete antigen, including the ability to induce immunization and/or to show protection against *S. pyogenes* e.g. in a sepsis and/or lethality model. The fragment of an antigen is functional active in the context of the present invention, if the activity of the fragment amounts to at least 10%, preferably at least 25%, more preferably at least 50%, even more preferably at least 70%, still more preferably at least 80%, especially at least 90%, particularly at least 95%, most preferably at least 99% of the activity of the antigen without sequence alteration. These fragments may be designed or obtained in any desired length, including as small as about 50 to 80 amino acids in length.

The functional active fragment may be also characterized by other structural features. Accordingly, in one preferred embodiment of the invention the functional active fragments consists of at least 60%, preferably at least 70%, more preferably at least 80%, still more

preferably at least 90%, even more preferably at least 95%, most preferably 99% of the amino acids of the antigen of any of the SEQ ID NOS: 1 to 7. The functional active fragment as defined above may be derived from the peptide by one or more amino acid deletions. The deletions may be C-terminally, N-terminally and/or internally.

Another preferred embodiment of the invention relates to a peptide as defined above in the previous embodiments, wherein the antigen is a functional active variant of an antigen of any of the SEQ ID NOS: 1 to 7 and wherein the variant has at least 50% sequence identity to the antigen of any of the SEQ ID NOS: 1 to 7. In a more preferred embodiment the functional active variant has a sequence identity of at least 60%, preferably at least 70%, more preferably at least 80%, still more preferably at least 90%, even more preferably at least 95%, most preferably 99% to the antigen of any of the SEQ ID NOS: 1 to 7.

The percentage of sequence identity can be determined e.g. by sequence alignment. Methods of alignment of sequences for comparison are well known in the art. Various programs and alignment algorithms have been described e.g. in Smith and Waterman, Adv. Appl. Math. 2: 482, 1981 or Pearson and Lipman, Proc. Natl. Acad. Sci. U.S.A. 85: 2444-2448, 1988.

The NCBI Basic Local Alignment Search Tool (BLAST) (Altschul et al., J. Mol. Biol. 215: 403-410, 1990) is available from several sources, including the National Center for Biotechnology Information (NCBI, Bethesda, MD) and on the Internet, for use in connection with the sequence analysis programs blastp, blastn, blastx, tblastn and tblastx. Variants of an antigen of any of the sequences of SEQ ID NOS: 1 to 7 are typically characterized using the NCBI Blast 2.0, gapped blastp set to default parameters. For comparisons of amino acid sequences of at least 35 amino acids, the Blast 2 sequences function is employed using the default BLOSUM62 matrix set to default parameters, (gap existence cost of 11, and a per residue gap cost of 1). When aligning short peptides (fewer than around 35 amino acids), the alignment is performed using the Blast 2 sequences function, employing the PAM30 matrix set to default parameters (open gap 9, extension gap 1 penalties). Methods for determining sequence identity over such short windows such as 15 amino acids or less are described at the website that is maintained by the National

Center for Biotechnology Information in Bethesda, Maryland (http://www.ncbi.nlm.nih.gov/BLAST/).

The functional active variant of an antigen is obtained by sequence alterations in the antigen, wherein the antigen with the sequence alterations retains a function of the unaltered antigen, e.g. having a biological activity similar to that displayed by the complete antigen, including the ability to induce an immune response and/or to show protection against *S. pyogenes* e.g. in a sepsis and/or lethality model. Such sequence alterations can include, but are not limited to, conservative substitutions, deletions, mutations and insertions. These characteristics of the functional active variant can be assessed e.g. as detailed in Example 1. In the context of the present invention a variant specifically has a biological activity similar to that displayed by the antigen without alteration, including the ability to induce an immune response and/or to show protection against *S. pyogenes* e.g. in a sepsis and/or lethality model if the activity of the variant amounts to at least 10%, preferably at least 25%, more preferably at least 50%, even more preferably at least 70%, still more preferably at least 80%, especially at least 90%, particularly at least 95%, most preferably at least 99% of the activity of the antigen without sequence alterations.

The term "functional active variant" includes naturally-occurring allelic variants, as well as mutants or any other non-naturally occurring variants. As is known in the art, an allelic variant is an alternate form of a (poly)peptide that is characterized as having a substitution, deletion, or addition of one or more amino acids that does essentially not alter the biological function of the polypeptide. By "biological function" is meant a function of the polypeptide in the cells in which it naturally occurs, even if the function is not necessary for the growth or survival of the cells. For example, the biological function of a porin is to allow the entry into cells of compounds present in the extracellular medium. The biological function is distinct from the antigenic function. A polypeptide can have more than one biological function.

Within any species of the living world, allelic variation is the rule. For example, any bacterial species, *e.g. S. pyogenes*, is usually represented by a variety of strains (characterized by clonal reproduction) that differ from each other by minor allelic variations. Indeed, a polypeptide that fulfils the same biological function in different

strains can have an amino acid sequence that is not identical in each of the strains. Such an allelic variation is equally reflected at the polynucleotide level.

Allelic variation is very common within the *S. pyogenes* species. Such allelic variation is also the basis for the molecular typing of group A streptococcal strains by emm typing as described above (see, e.g. Facklam, R. et al. (1999) Emerg Infect Dis. 5: 247-53 or http://www.cdc.gov/ncidod/biotech/strep/emmtypes.htm). Further, genes such as *sic* are subject to allelic variation (Hoe N., et al. (2001) J. Inf. Dis. **183**: 633-9). However, proteins with large allelic variation are in general not suitable candidates for a vaccine, as immunization would not protect against infection with all strains, or alternative immunization would possibly induce the emergence of new allelic variants not covered by the vaccine.

In a preferred embodiment, the functional active variant or fragment derived from the antigen by amino acid exchanges, deletions or insertions may also conserve, or more preferably improve, the activity (as defined above). Furthermore, these peptides may also cover epitopes, which trigger the same or preferably an improved T cell response. These epitope are referred to as "heteroclitic". They have a similar or preferably greater affinity to MHC/HLA molecules, and the ability to stimulate the T cell receptors (TCR) directed to the original epitope in a similar or preferably stronger manner. Heteroclitic epitopes can be obtained by rational design i. e. taking into account the contribution of individual residues to binding to MHC/HLA as for instance described by (Rammensee, H. et al., 1999, Immunogenetics. 50: 213-219), combined with a systematic exchange of residues potentially interacting with the TCR and testing the resulting sequences with T cells directed against the original epitope. Such a design is possible for a skilled man in the art without much experimentation.

In a still more preferred embodiment of the invention the functional active variant of an antigen of any of the SEQ ID NOS: 1 to 7 having at least 50% sequence identity to the antigen of any of the SEQ ID NOS: 1 to 7, especially at least 60%, preferably at least 70%, more preferably at least 80%, still more preferably at least 90%, even more preferably at least 95%, most preferably 99% to the antigen of any of the SEQ ID NOS: 1 to 7 is derived from the antigen of any of the sequences of SEQ ID NOS: 1 to 7 by conservative

substitutions. Conservative substitutions are those that take place within a family of amino acids that are related in their side chains and chemical properties. Examples of such families are amino acids with basic side chains, with acidic side chains, with non-polar aliphatic side chains, with non-polar aromatic side chains, with uncharged polar side chains, with small side chains, with large side chains etc.. In one embodiment, one conservative substitution is included in the peptide. In another embodiment, two conservative substitutions or less are included in the peptide. In a further embodiment, three conservative substitutions or less are included in the peptide.

Examples of conservative amino acid substitutions include, but are not limited to, those listed below:

Original Residue	Conservative Substitutions
Ala	Ser
Arg	Lys
Asn	Gln; His
Asp	Glu
Cys	Ser
Gln	Asn
Glu	Asp
His	Asn; Gln
Ile	Leu, Val
Leu	Ile; Val
Lys	Arg; Gln; Asn
Met	Leu; Ile
Phe	Met; Leu; Tyr
Ser	Thr
Thr	Ser
Trp	Tyr
Tyr	Trp; Phe
Val	Ile; Leu

Examples of suitable variants of the peptide of the invention obtained by one or more amino acid exchange(s), deletion(s) and/or insertion(s) may be derived from data provided in tables 5 to 7 and 9. Particularly, tables 5 to 7 and 9 list naturally occurring amino acid alterations (substitutions, insertions, deletions) at particular positions in comparison to *S. pyrogenes* SF370.

With respect to a variant of a peptide having (i.e. consisting of or comprising as defined above, particularly as defined in the above items (a) to (f)) SEQ ID NO: 1, the variant of the invention may differ from the peptide having SEQ ID NO: 1 by one or more of the alterations identified in table 5.

With respect to a variant of a peptide having (i.e. consisting of or comprising as defined above, particularly as defined in the above items (a) to (f)) SEQ ID NO: 2, the variant of the invention may differ from the peptide having SEQ ID NO: 2 by one or more of the alterations identified in table 6.

With respect to a variant of a peptide having (i.e. consisting of or comprising as defined above, particularly as defined in the above items (a) to (f)) SEQ ID NO: 3, the variant of the invention may differ from the peptide having SEQ ID NO: 3 by one or more of the alterations identified in table 6.

With respect to a variant of a peptide having (i.e. consisting of or comprising as defined above, particularly as defined in the above items (a) to (f)) SEQ ID NO: 4, the variant of the invention may differ from the peptide having SEQ ID NO: 4 by one or more of the alterations identified in table 7.

With respect to a variant of a peptide having (i.e. consisting of or comprising as defined above, particularly as defined in the above items (a) to (f)) SEQ ID NO: 5, the variant of the invention may differ from the peptide having SEQ ID NO: 5 by one or more of the alterations identified in table 7.

With respect to a variant of a peptide having (i.e. consisting of or comprising as defined above, particularly as defined in the above items (a) to (f)) SEQ ID NO: 6, the variant of

the invention may differ from the peptide having SEQ ID NO: 6 by one or more of the alterations identified in table 7.

With respect to a variant of a peptide having (i.e. consisting of or comprising as defined above, particularly as defined in the above items (a) to (f)) SEQ ID NO: 7, the variant of the invention may differ from the peptide having SEQ ID NO: 7 by one or more of the alterations identified in table 9.

It should be understood that variants obtained from a peptide of the invention by one or more sequence alterations in accordance with tables 5 to 7 and 9 are preferred.

A further aspect of the present invention describes a peptide comprising an amino acid sequence with at least 95% sequence identity to at least one of SEQ ID NO: 1, 2, 3, 4, 5, 6 or 7. In different embodiment the peptide comprises, consists, or consists essentially of a region of at least 95%, at least 97% or at least 99% identical to SEQ ID NO: 1, 2, 3, 4, 5, 6 or 7, or differs by 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acid alteration(s). In one embodiment the term "consist" may be as defined in the above items (a) to (f)). Preferably, the peptide does not contain a full-length naturally occurring Spy0269, Spy0292, Spy0416A (amino acids 33-867), or Spy0872.

SEQ ID NO: 1, 2, 3, 4, 5, 6 or 7 provide core sequences useful for producing a protective immune response. SEQ ID NO: 1 provides an amino acid core from amino acids 37-488 of Spy0269. SEQ ID NO: 2 provides a core region of amino acids 23-184 of Spy0292. SEQ ID NO: 3 provides a core of amino acids 23-300 of Spy0292, which is a longer-length sequence containing the shorter-length core sequence of 23-184 of Spy0292 provided in SEQ ID NO: 2. Surprisingly, the shorter fragment Spy0292-1 (SEQ ID NO: 2) shows even greater protection in the mouse model compared to the longer fragment Spy0292-3 (SEQ ID NO: 3), as depicted in Figure 1. As described above, smaller peptides are in general advantageous over larger ones, since they may be produced in a more economic manner, they reduce the probability of inducing antibodies which can cause cross-reactions with human tissues, and they facilitate the preparation of combination vaccines comprising more than one antigen. SEQ ID NO: 4, 5, and 6 provide different Spy0416A core sequences of varying activity. SEQ ID NO: 5 provides a common core of amino acids 148-

458 of Spy0416A and has the lowest activity. SEQ ID NO: 6 provides a core sequence containing amino acids 72-558 of Spy0416A with greater activity than the shorter core. SEQ ID NO: 4 provides an amino acid core containing amino acids 34-677 of Spy0416, also with activity greater than the 148-458 core.

Based on the guidance provided herein different peptides can be designed taking into account the core sequences provided in SEQ ID NOs: 1-7. Such guidance includes structurally related peptides containing (1) internal alterations; (2) additional amino acid groups at the amino and/or carboxyl terminus; and/or (3) additional modification(s) as described herein.

For structurally related peptides, each amino acid alteration is independently either an addition, substitution, or deletion. In a further embodiment, the amino terminus is methionine. The presence of methionine may be useful for recombinant expression. In some cases, the methionine may be initially present as a result of translation and subsequently cleaved. Additional examples and embodiments, including broader embodiments and some further descriptions applicable for structurally related peptides such as functional variants are provided above, particularly in the description of functional active variants.

In another subject of the invention the peptide as described above comprises or consists of at least 2, preferably at least 3, more preferably at least 4 antigens as defined above. If two ore more peptides derived from the same full length sequence (e.g Spy0292 or Spy0416) are combined into one peptide, these sequences do preferably not overlap. In one embodiment the term "consist" may be as defined in the above items (a) to (f)).

In another embodiment of the invention the peptide as defined above may be modified by one or more of a variety of chemical techniques to produce derivatives having essentially the same activity (as defined above for fragments and variants) as the modified peptides, and optionally having other desirable properties. For example, carboxylic acid groups of the protein, whether C-terminal or side chain, may be provided in the form of a salt of a pharmaceutically-acceptable cation or esterified to form an ester, or converted to an amide. Amino groups of the peptide, whether amino-terminal or side chain, may be in the form of

a pharmaceutically-acceptable acid addition salt, such as the HCl, HBr, acetic, benzoic, toluene sulfonic, maleic, tartaric and other organic salts, or may be converted to an amide. Hydroxyl groups of the peptide side chains may be converted to alkoxy or to an ester using well recognized techniques. Phenyl and phenolic rings of the peptide side chains may be substituted with one or more halogen atoms, such as fluorine, chlorine, bromine or iodine, or with alkyl, alkoxy, carboxylic acids and esters thereof, or amides of such carboxylic acids. Thiols can be protected with any one of a number of well recognized protecting groups, such as acetamide groups.

Peptides of this invention may be in combination with outer surface proteins or other proteins or antigens of other proteins. In such combination, the antigen may be in the form of a fusion protein. The antigen of the invention may be optionally fused to a selected peptide or protein derived from other microorganisms. For example, an antigen or polypeptide of this invention may be fused at its N-terminus or C-terminus to a polypeptide from another pathogen or to more than one polypeptide in sequence. Peptides which may be useful for this purpose include polypeptides identified by the prior art.

In an embodiment of the invention the peptide of the invention is fused to an epitope tag which provides an epitope to which an anti-tag substance can selectively bind. The epitope tag is generally placed at the amino- or carboxyl-terminus of the peptide but may be incorporated as an internal insertion or substitution as the biological activity permits. The presence of such epitope-tagged forms of a peptide can be detected using a substance such as an antibody against the tagged peptide. Also, provision of the epitope tag enables the peptide to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag. Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine (poly-his), poly-histidine-glycine (poly-his-gly) tags, the HA tag polypeptide, the c-myc tag, the Strep tag and the FLAG tag.

Fusions also may include the peptides or antigens of this invention fused or coupled to moieties other than amino acids, including lipids and carbohydrates. Further, antigens of this invention may be employed in combination with other vaccinal agents described by the prior art, as well as with other species of vaccinal agents derived from other

microorganisms. Such proteins are useful in the prevention, treatment and diagnosis of diseases caused by a wide spectrum of Streptococcus isolates.

These fusion proteins are constructed for use in the methods and compositions of this invention. These fusion proteins or multimeric proteins may be produced recombinantly, or may be synthesized chemically.

The peptides of the invention may be prepared by any of a number of conventional techniques. Desired peptides may be chemically synthesized. An alternative approach involves generating the fragments of known peptides by enzymatic digestion, e.g., by treating the protein with an enzyme known to cleave proteins at sites defined by particular amino acid residues, or by digesting the DNA with suitable restriction enzymes, expressing the digested DNA and isolating the desired fragment. Yet another suitable technique involves isolating and amplifying a DNA fragment encoding a desired peptide fragment, by polymerase chain reaction (PCR). Oligonucleotides that define the desired termini of the DNA fragment are employed as the 5' and 3' primers in the PCR. Techniques for making mutations, such as deletions, insertions and substitutions, at predetermined sites in DNA, and therefore in proteins, having a known sequence are well known. One of skill in the art using conventional techniques, such as PCR, may readily use the antigens and peptides provided herein to identify and isolate other similar proteins. Such methods are routine and not considered to require undue experimentation, given the information provided herein. For example, variations can be made using oligonucleotide-mediated site-directed mutagenesis (Carter et al., Nucl. Acids Res., 13: 4431 (1985); Zoller et al., Nucl. Acids Res. 10: 6487 (1987)), cassette mutagenesis (Wells et al., Gene, 34: 315 (1985)), restriction selection mutagenesis (Wells et al., Philos. Trans. R. Soc. London SerA, 317: 415 (1986)), PCR mutagenesis, or other known techniques can be performed on the cloned DNA to produce the peptide of the invention.

Another subject of the present invention relates to a nucleic acid encoding a peptide of the invention, i.e. any peptide as defined above, or a nucleic acid complementary thereto. Nucleic acid molecules of the present invention may be in the form of RNA, such as mRNA or cRNA, or in the form of DNA, including, for instance, cDNA and genomic DNA e.g. obtained by cloning or produced by chemical synthetic techniques or by a

combination thereof. The DNA may be double- stranded or single-stranded. Single-stranded DNA may be the coding strand, also known as the sense strand, or it may be the non-coding strand, also referred to as the anti-sense strand. Nucleic acid molecule as used herein also refers to, among other, single- and double- stranded DNA, DNA that is a mixture of single- and double-stranded RNA, and RNA that is a mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded, or a mixture of single- and double-stranded regions.

The nucleic acid may be a fragment of a nucleic acid occurring naturally in *S. pyogenes*, especially in *S. pyogenes* serotype M1, M2, M3, M4, M5, M6, M11, M12, M14, M19, M22, M24, M25, M28, M44, M49, M57, M59, M60, M61, M76, M83, M84, M87, M89 or M118, particularly *S. pyogenes* SF370. Preferably the nucleic acid has a sequence as defined in any of the sequences of SEQ ID NOS: 11 to 17 or of any of the homologous variants identified in the attached listing of nucleic acid sequence data. Examples of homologous sequences of a different serotype are those listed below:

Full length nucleic acid sequence (SEQ ID NO)	**Nucleic acid of the invention (SEQ ID NO)**	**Homologous nucleic acid sequences (SEQ ID NOS)**
133	11	134 to 143
144	12	145 to 154
144	13	155 to 164
165	14	166 to 175
165	15	176 to 185
165	16	186 to 195
196	17	197 to 206

The nucleic acid also includes sequences that are a result of the degeneration of the genetic code. There are 20 natural amino acids, most of which are specified by more than one codon. Therefore, all nucleotide sequences are included in the invention which result in the peptide as defined above.

Additionally, the nucleic acid may contain one or more modified bases. Such nucleic acids may also contain modifications e.g. in the ribose-phosphate backbone to increase stability and half life of such molecules in physiological environments. Thus, DNAs or RNAs with backbones modified for stability or for other reasons are "nucleic acid molecule" as that feature is intended herein. Moreover, DNAs or RNAs comprising unusual bases, such as inosine, or modified bases, such as tritylated bases, to name just two examples, are nucleic acid molecule within the context of the present invention. It will be appreciated that a great variety of modifications have been made to DNA and RNA that serve many useful purposes known to those of skill in the art. The term nucleic acid molecule as it is employed herein embraces such chemically, enzymatically or metabolically modified forms of nucleic acid molecule, as well as the chemical forms of DNA and RNA characteristic of viruses and cells, including simple and complex cells, *inter alia*. For example, nucleotide substitutions can be made which do not affect the polypeptide encoded by the nucleic acid, and thus any nucleic acid molecule which encodes an antigen or fragment or functional active variant thereof as defined above is encompassed by the present invention.

Furthermore, any of the nucleic acid molecules encoding an antigen of the invention or fragment or functional active variant thereof can be functionally linked, using standard techniques such as standard cloning techniques, to any desired regulatory sequences, whether a *S. pyogenes* regulatory sequence or a heterologous regulatory sequence, heterologous leader sequence, heterologous marker sequence or a heterologous coding sequence to create a fusion protein.

The nucleic acid of the invention may be originally formed *in vitro* or in a cell in culture, in general, by the manipulation of nucleic acids by endonucleases and/or exonucleases and/or polymerases and/or ligases and/or recombinases or other methods known to the skilled practitioner to produce the nucleic acids.

In one embodiment of the invention the nucleic acid is located in a vector. A vector may additionally include nucleic acid sequences that permit it to replicate in the host cell, such as an origin of replication, one or more desired genes and/or selectable marker genes and other genetic elements known in the art such as regulatory elements directing transcription,

translation and/or secretion of the encoded protein. The vector may be used to transduce, transform or infect a cell, thereby causing the cell to express inserted nucleic acids and/or proteins other than those native to the cell. The vector optionally includes materials to aid in achieving entry of the nucleic acid into the cell, such as a viral particle, liposome, protein coating or the like. Numerous types of appropriate expression vectors are known in the art for protein expression, by standard molecular biology techniques. Such vectors are selected from among conventional vector types including insects, e.g., baculovirus expression, or yeast, fungal, bacterial or viral expression systems. Other appropriate expression vectors, of which numerous types are known in the art, can also be used for this purpose. Methods for obtaining such expression vectors are well-known (see, e.g. Sambrook et al, Molecular Cloning. A Laboratory Manual, 2nd edition, Cold Spring Harbor Laboratory, New York (1989)). In one embodiment, the vector is a viral vector. Viral vectors include, but are not limited to, retroviral and adenoviral vectors.

Suitable host cells or cell lines for transfection by this method include bacterial cells. For example, the various strains of *E. coli* are well-known as host cells in the field of biotechnology. Various strains of *B. subtilis*, *Pseudomonas*, *Streptomyces*, and other bacilli and the like may also be employed in this method. Many strains of yeast cells known to those skilled in the art are also available as host cells for expression of the peptides of the present invention. Other fungal cells or insect cells such as *Spodoptera frugipedera* (Sf9) cells may also be employed as expression systems. Alternatively, mammalian cells, such as human 293 cells, Chinese hamster ovary cells (CHO), the monkey COS-1 cell line or murine 3T3 cells derived from Swiss, BALB/c or NIH mice may be used. Still other suitable host cells, as well as methods for transfection, culture, amplification, screening, production, and purification are known in the art.

A peptide of the invention may be produced by expressing a nucleic acid of the invention in a suitable host cell. The host cells can be transfected, e.g. by conventional means such as electroporation with at least one expression vector containing a nucleic acid of the invention under the control of a transcriptional regulatory sequence. The transfected or transformed host cell is then cultured under conditions that allow expression of the protein. The expressed protein is recovered, isolated, and optionally purified from the cell (or from the culture medium, if expressed extracellularly) by appropriate means known to one of

skill in the art. For example, the proteins are isolated in soluble form following cell lysis, or extracted using known techniques, e.g. in guanidine chloride. If desired, the peptides or fragments of the invention are produced as a fusion protein. Such fusion proteins are those described above. Alternatively, for example, it may be desirable to produce fusion proteins to enhance expression of the protein in a selected host cell or to improve purification. The molecules comprising the peptides and antigens of this invention may be further purified using any of a variety of conventional methods including, but not limited to: liquid chromatography such as normal or reversed phase, using HPLC, FPLC and the like; affinity chromatography (such as with inorganic ligands or monoclonal antibodies); size exclusion chromatography; immobilized metal chelate chromatography; gel electrophoresis; and the like. One of skill in the art may select the most appropriate isolation and purification techniques without departing from the scope of this invention. Such purification provides the antigen in a form substantially free from other proteinaceous and non-proteinaceous materials of the microorganism.

Another subject of the invention is a pharmaceutical composition, especially a vaccine, comprising

(i) at least one peptide according to the invention, and/or

(ii) at least one peptide comprising or consisting of the sequence of any of the SEQ ID NO: 8, SEQ ID NO: 9, or SEQ ID NO: 10, or a functional active variant thereof, and

(iii) optionally a pharmaceutically acceptable carrier or excipient.

The variants of the peptides of (ii) are as defined and may be obtained as the peptides of (i) (see above description of the peptides of the invention). Preferred alterations of the sequences of SEQ ID NO: 8 or 10 are those listed in tables 8 and 9, respectively.

The peptides of (i) and (ii) are referred to as pharmaceutical peptides of the invention.

With respect to the peptide of (ii), these proteins have been shown for the first time to be capable to provide protection against lethal *S. pyogenes* challenge (see Example 1), particularly in a physiologically highly relevant intranasal challenge model. Especially protein Spy0895 (SEQ ID NO: 9) shows particular promise as a vaccine candidate, because it provided protection against group A streptococcal infection in all three models listed in Table 1.

A pharmaceutical peptide of the invention may be used for methods for immunizing or treating humans and/or animals with the disease caused by infection with *S. pyogenes*. Therefore, the pharmaceutical peptide may be used within a pharmaceutical composition. The pharmaceutical composition of the present invention may further encompass pharmaceutically acceptable carriers and/or excipients. The pharmaceutically acceptable carriers and/or excipients useful in this invention are conventional and may include buffers, stabilizers, diluents, preservatives, and solubilizers. Remington's Pharmaceutical Sciences, by E. W. Martin, Mack Publishing Co., Easton, PA, 15th Edition (1975), describes compositions and formulations suitable for pharmaceutical delivery of the (poly)peptides herein disclosed. In general, the nature of the carrier or excipients will depend on the particular mode of administration being employed. For instance, parenteral formulations usually comprise injectable fluids that include pharmaceutically and physiologically acceptable fluids such as water, physiological saline, balanced salt solutions, aqueous dextrose, glycerol or the like as a vehicle. For solid compositions (e. g. powder, pill, tablet, or capsule forms), conventional non-toxic solid carriers can include, for example, pharmaceutical grades of mannitol, lactose, starch, or magnesium stearate. In addition to biologically neutral carriers, pharmaceutical compositions to be administered can contain minor amounts of non-toxic auxiliary substances, such as wetting or emulsifying agents, preservatives, and pH buffering agents and the like, for example sodium acetate or sorbitan monolaurate.

In a preferred embodiment the pharmaceutical composition further comprises an immunostimulatory substance such as an adjuvant. The adjuvant can be selected based on the method of administration and may include mineral oil-based adjuvants such as Freund's complete and incomplete adjuvant, Montanide incomplete Seppic adjuvant such as ISA, oil in water emulsion adjuvants such as the Ribi adjuvant system, syntax adjuvant formulation containing muramyl dipeptide, IC31™ (Intercell; a synthetic adjuvant comprising the peptide motif KLK [WO 02/32451] and an oligonucleotide [WO 01/93905]), or aluminum salt adjuvants. Preferably, the adjuvant is a mineral oil-based adjuvant, most preferably ISA206 (SEPPIC, Paris, France).

In other embodiments the immunostimulatory substance is selected from the group comprising polycationic polymers, especially polycationic peptides such as polyarginine, immunostimulatory deoxynucleotides (ODNs), especially Oligo(dIdC)$_{13}$, peptides containing at least two LysLeuLys motifs, especially KLKLLLLLKLK (SEQ ID NO: 55), neuroactive compounds, especially human growth hormone, alum, adjuvants or combinations thereof. In further embodiments, the combination is either a polycationic polymer and immunostimulatory deoxynucleotides or of a peptide containing at least two LysLeuLys motifs and immunostimulatory deoxynucleotides. In a still another embodiment the polycationic polymer is a polycationic peptide.

The term "Oligo(dIdC)$_{13}$" as used in the present invention means a phosphodiester backboned single-stranded DNA molecule containing 13 deoxy (inosine-cytosine) motifs, also defined by the term [oligo-d(IC)$_{13}$]. The exact sequence is 5'-dIdCdIdCdIdCdIdCdIdCdIdCdIdCdIdCdIdCdIdCdIdCdIdC-3'. Oligo(dIdC)$_{13}$ can also be defined by the terms (oligo-dIC$_{26}$); oligo-dIC$_{26\text{-mer}}$; oligo-deoxy IC, 26-mer; or oligo-dIC, 26-mer, as specified for example in WO 01/93903 and WO 01/93905.

In an embodiment the immunostimulatory substance is at least one immunostimulatory nucleic acid. Immunostimulatory nucleic acids are e.g. neutral or artificial CpG containing nucleic acids, short stretches of nucleic acids derived from non-vertebrates or in form of short oligonucleotides (ODNs) containing non-methylated cytosine-guanine dinucleotides (CpG) in a defined base context (e.g. as described in WO 96/02555). Alternatively, also nucleic acids based on inosine and cytidine as e.g. described in WO 01/93903, or deoxynucleic acids containing deoxy-inosine and/or deoxyuridine residues (described in WO 01/93905 and WO 02/095027) may preferably be used as immunostimulatory nucleic acids in the present invention. Preferably, mixtures of different immunostimulatory nucleic acids are used in the present invention. Additionally, the aforementioned polycationic compounds may be combined with any of the immunostimulatory nucleic acids as aforementioned. Preferably, such combinations are according to the ones described in WO 01/93905, WO 02/32451, WO 01/54720, WO 01/93903, WO 02/13857, WO 02/095027 and WO 03/047602.

In addition or alternatively, such pharmaceutical or vaccine composition may comprise a neuroactive compound. Preferably, the neuroactive compound is human growth factor, e.g. described in WO 01/24822. Also preferably, the neuroactive compound is combined with any of the polycationic compounds and/or immunostimulatory nucleic acids as defined above.

The composition may be used e.g. for immunization or treatment of a subject. The pharmaceutical composition encompasses at least one pharmaceutical peptide of the invention; however, it may also contain a cocktail (i.e., a simple mixture) containing different pharmaceutical peptides (including fragments and other variants) of the invention, optionally mixed with different antigenic proteins or peptides of other pathogens. Such mixtures of these peptides, polypeptides, proteins or fragments or variants thereof are useful e.g. in the generation of desired antibodies to a wide spectrum of Streptococci isolates. The pharmaceutical peptide(s) of the present invention may also be used in the form of a pharmaceutically acceptable salt. Suitable acids and bases which are capable of forming salts with the peptides of the present invention are well known to those of skill in the art, and include inorganic and organic acids and bases.

Still another subject of the invention is a pharmaceutical composition containing a nucleic acid selected from the group consisting of:

(i) a nucleic acid of the invention and/or a nucleic acid complementary thereto, and/or

(ii) a nucleic acid coding for the peptide comprising or consisting of the sequence of any of the SEQ ID NO: 8, SEQ ID NO: 9, or SEQ ID NO: 10, particularly a DNA sequence of any of the SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 20, or a functional active variant thereof or a nucleic acid complementary thereto or the corresponding RNA sequence, and

(iii) optionally a pharmaceutically acceptable carrier or excipient.

The variants of the nucleic acids of (ii) are as defined and may be obtained as the nucleic acids of (i) (see above description of the nucleic acids of the invention). The nucleic acids of (i) and (ii) are referred to as pharmaceutical nucleic acids of the invention.

The pharmaceutical nucleic acid sequences, alone or in combination with other nucleic acid sequences encoding antigens or antibodies or directed to other pathogenic microorganisms, may further be used as components of a pharmaceutical composition. The composition may be used for immunizing or treating humans and/or animals being susceptible to or having a disease caused by infection with *S. pyogenes*, particularly *S. pyogenes* serotype M1, M2, M3, M4, M5, M6, M11, M12, M14, M19, M22, M24, M25, M28, M44, M49, M57, M59, M60, M61, M76, M83, M84, M87, M89 or M118, especially *S. pyogenes* SF370. The pharmaceutically acceptable carrier or excipient may be as defined above.

In another embodiment, the pharmaceutical nucleic acids of this invention, alone or in combination with nucleic acid sequences encoding other antigens or antibodies from other pathogenic microorganisms, may further be used in compositions directed to actively induce a protective immune response in a subject to the pathogen. These components of the present invention are useful in methods for inducing a protective immune response in humans and/or animals against infection with *S. pyogenes*, particularly with *S. pyogenes* serotype M1, M2, M3, M4, M5, M6, M11, M12, M14, M19, M22, M24, M25, M28, M44, M49, M57, M59, M60, M61, M76, M83, M84, M87, M89 or M118, especially *S. pyogenes* SF370.

For use in the preparation of the therapeutic or vaccine compositions, nucleic acid delivery compositions and methods are useful, which are known to those of skill in the art. The pharmaceutical nucleic acid of the invention may be employed in the methods of this invention or in the compositions described herein as DNA sequences, either administered as naked DNA, or associated with a pharmaceutically acceptable carrier and provide for *in vivo* expression of the antigen, peptide or polypeptide. So-called "naked DNA" may be used to express the antigen, peptide or polypeptide of the invention *in vivo* in a patient. (See, e.g., J. Cohen, Science, 259: 1691-1692, which describes similar uses of "naked DNA"). For example, "naked DNA" associated with regulatory sequences may be administered therapeutically or as part of the vaccine composition e.g., by injection.

Alternatively, a nucleic acid, especially a pharmaceutical nucleic acid according to the invention, encoding an antigen or peptide of the invention or a nucleic acid complementary

thereto may be used within a pharmaceutical composition, e.g. in order to express the antigen or (pharmaceutical) peptide of the invention *in vivo*, e.g., to induce antibodies.

A preferred embodiment of the invention relates to a pharmaceutical composition, wherein the pharmaceutical nucleic acid according to the invention is comprised in a vector and/or a cell. Vectors and cells suitable in the context of the present invention are described above. Vectors are particularly employed for a DNA vaccine. An appropriate vector for delivery may be readily selected by one of skill in the art. Exemplary vectors for *in vivo* gene delivery are readily available from a variety of academic and commercial sources, and include, e.g., adeno-associated virus (International patent application No. PCT/US91/03440), adenovirus vectors (M. Kay et al, Proc. Natl. Acad. Sci. USA, 91: 2353 (1994); S. Ishibashi et al, J. Clin. Invest., 92: 883 (1993)), or other viral vectors, e.g., various poxviruses, vaccinia, etc.. Recombinant viral vectors, such as retroviruses or adenoviruses, are preferred for integrating the exogenous DNA into the chromosome of the cell.

Another subject of the invention relates to an antibody or functional active fragment thereof which binds specifically to the antigen of the invention. The present invention includes, for example, monoclonal and polyclonal antibodies, chimeric, single chain, and humanized antibodies, as well as Fab fragments, or the product of a Fab expression library.

While *S. pyogenes* infections are primarily a disease of children and cause non-severe diseases such as bacterial pharyngitis and impetigo, GAS are also responsible for streptococcal toxic shock syndrome associated necrotizing fasciitis (Cone, L., et al. (1987). New Engl J Med 317: 146-9; Stevens, D. (1992). Clin Infect Dis 14: 2-11) and several post-streptococcal sequelae such as acute rheumatic fever, acute glomerulonephritis and reactive arthritis. It would be very beneficial to provide monoclonal or polyclonal antibody therapies which target antigenic proteins of *S. pyogenes* and have the potential to support a therapy of an infection or eliminate the pathogen and the disease altogether.

In a preferred embodiment the antibody is a monoclonal, polyclonal, chimeric or humanized antibody or functional active variant thereof. In another preferred embodiment the functional active fragment comprises a Fab fragment.

Antibodies generated against the antigens, fragments or variants thereof of the present invention can be obtained by direct injection of the antigens, fragments or variants thereof into an animal or by administering the antigens, fragments or variants thereof to an animal, preferably a non-human. The antibody so obtained will then bind the antigens, fragments or variants. Such antibodies can then be used to isolate reactive antigens, fragments or variants thereof from tissue expressing those.

For preparation of monoclonal antibodies, any technique known in the art, which provides antibodies produced by continuous cell line cultures, e.g. a hybridoma cell line, can be used.

Techniques described for the production of single chain antibodies (U. S. Patent No. 4,946,778) can be adapted to produce single chain antibodies to the antigens, fragments or variants thereof according to this invention. Also, transgenic mice or other organisms such as other mammals may be used to express humanized antibodies to antigens, fragments or variants thereof according to this invention.

Still another subject of the invention relates to a hybridoma cell line which produces the antibody of the invention.

Hybridoma cell lines expressing desirable monoclonal antibodies are generated by well-known conventional techniques. The hybridoma cell can be generated by fusing a normal-activated, antibody-producing B cell with a myeloma cell. In the context of the present invention the hybridoma cell is able to produce an antibody specifically binding to the antigen of the invention.

Similarly, desirable high titre antibodies are generated by applying known recombinant techniques to the monoclonal or polyclonal antibodies developed to these antigens (see, e.g., PCT Patent Application No. PCT/GB85/00392; British Patent Application Publication No. GB2188638A; Amit et al., Science, 233: 747-753 (1986); Queen et al., Proc. Natl. Acad. Sci. USA, 86: 10029-10033 (1989); PCT Patent Application No. WO90/07861;

Riechmann et al., Nature, 332: 323-327 (1988); Huse et al., Science, 246: 1275-1281 (1988)).

The present invention also provides a method for producing an antibody according to the invention, characterized by the following steps:

(a) administering an effective amount of the peptide according to the invention to an animal; and

(b) isolating the antibody produced by the animal in response to the administration of step (a) from the animal.

Another subject of the invention relates to a method for producing an antibody according to the invention, characterized by the following steps:

(a) contacting a B cell with an effective amount of the peptide according to the invention;

(b) fusing the B cell of step (a) with a myeloma cell to obtain a hybridoma cell; and

(c) isolating the antibody produced by the cultivated hybridoma cell.

More particularly, the antibody may be produced by initiating an immune response in a non-human animal by administrating a peptide of the invention to an animal, removing an antibody containing body fluid from said animal, and producing the antibody by subjecting said antibody containing body fluid to further purification steps. Alternatively, the antibody may be produced by initiating an immune response in a non-human animal by administrating an antigen, fragment or variant thereof, as defined in the present invention, to said animal, removing the spleen or spleen cells from said animal and/or producing hybridoma cells of said spleen or spleen cells, selecting and cloning hybridoma cells specific for said antigen, fragment or variant thereof and producing the antibody by cultivation of said cloned hybridoma cells.

In a preferred embodiment the antibody produced according to a method of the invention is additionally purified. Methods of purification are known to the skilled artisan.

The antibody may be used in methods for preventing or treating an infection. Accordingly, still another subject of the invention relates to a pharmaceutical composition, especially a

vaccine, comprising an antibody of the invention. The pharmaceutical composition may encompass further components as detailed above. The composition may further encompass substances increasing their capacity to stimulate T cells. These include T helper cell epitopes, lipids or liposomes or preferred modifications as described in WO01/78767. Another way to increase the T cell stimulating capacity of epitopes is their formulation with immune stimulating substances for instance cytokines or chemokines like interleukin-2, -7, -12, -18, class I and II interferons (IFN), especially IFN-gamma, GM-CSF, TNF-alpha, flt3-ligand and others.

A further subject of the invention relates to a pharmaceutical composition comprising the pharmaceutical peptide of the invention or the pharmaceutical nucleic acid of the invention or an antibody of the invention or functional fragment thereof for the immunization of a subject against an infection or the treatment of a subject having an infection, wherein the infection is preferably a *S. pyogenes* infection. In another aspect of the invention a pharmaceutical peptide of the invention or a pharmaceutical nucleic acid of the invention or an antibody of the invention or functional fragment thereof is used for the manufacture of a medicament for the immunization of a subject against an infection or the treatment of a subject having an infection, wherein the infection is preferably a *S. pyogenes* infection, more preferably an infection with *S. pyogenes* serotype M1, M2, M3, M4, M5, M6, M11, M12, M14, M19, M22, M24, M25, M28, M44, M49, M57, M59, M60, M61, M76, M83, M84, M87, M89 or M118, especially *S. pyogenes* SF370. Alternatively, a pharmaceutical peptide or a pharmaceutical nucleic acid of the invention or an antibody of the invention or functional fragment thereof is used in a method of immunizing or treating a subject in need thereof, wherein an effective amount of the pharmaceutical peptide or the pharmaceutical nucleic acid of the invention or an antibody of the invention or functional fragment thereof is administered to the subject. The subject may be immunized in order to prevent an infection, particularly a *S. pyogenes* infection, or may be treated to ameliorate or cure an infection, particularly a *S. pyogenes* infection. The determination of the effective amount to be administered is within the knowledge of the skilled practitioner. Exemplary amounts are mentioned below.

The pharmaceutical peptides or the pharmaceutical nucleic acids of the invention are generally useful for inducing an immune response in a subject. The vaccine used for

immunization may be administered to a subject susceptible to infection by *S. pyogenes*, preferably mammals, and still more preferably humans. Potential modes of administration include oral, intranasal, intramuscular, intra-lymph node, intradermal, intraperitoneal, subcutaneous, and combinations thereof, but most preferably intramuscular injection. The volume of the dose for intramuscular administration is preferably up to about 5 mL, for example, between 0.3 mL and 3 mL, between 1 mL and 3 mL, about 0.5 to 1 mL, or about 2 mL. The amount of protein comprising the antigen in each dose should be enough to confer effective immunity to decrease the risk of developing clinical signs, e.g. resulting from *S. pyogenes* infection. In different embodiments, the unit dose of protein should be up to about 5 μg protein/kg body weight, between about 0.2 to 3 μg, between about 0.3 to 1.5 μg, between about 0.4 to 0.8 μg, or about 0.6 μg. In alternative embodiments unit doses of protein could be up to about 6 μg protein/kg body weight, between about 0.05 to 5 μg, or between about 0.1 to 4 μg. In different embodiments, the dose is administered 1 to 3 times, e.g. with an interval of 1 to 3 weeks. Representative amounts of protein per dose are from approximately 1 μg to approximately 1 mg, more preferably from approximately 5 μg to approximately 500 μg, still more preferably from approximately 10 μg to approximately 250 μg and most preferably from approximately 25 μg to approximately 100 μg.

In still another aspect of the invention the antibody of the invention or functional fragment thereof is used for the manufacture of a medicament for the treatment of an infection, preferably a *S. pyogenes* infection, more preferably an infection with *S. pyogenes* serotype M1, M2, M3, M4, M5, M6, M11, M12, M14, M19, M22, M24, M25, M28, M44, M49, M57, M59, M60, M61, M76, M83, M84, M87, M89 or M118, especially *S. pyogenes* SF370. Alternatively, the antibody of the invention is used in a method of treating a subject in need thereof, wherein an effective amount of the antibody of the invention is administered to the subject. The subject may be treated to ameliorate or cure an infection, particularly a *S. pyogenes* infection. The determination of the effective amount to be administered is within the knowledge of the skilled practitioner.

The treatment involves administering an effective amount of an antibody of the invention to a subject, preferably a mammal, more preferably a human. Thus, antibodies against the antigens, fragments or variants thereof of the present invention may be employed to inhibit and/or treat infections, particularly bacterial infections and especially infections arising

from *S. pyogenes*, especially *S. pyogenes* serotype M1, M2, M3, M4, M5, M6, M11, M12, M14, M19, M22, M24, M25, M28, M44, M49, M57, M59, M60, M61, M76, M83, M84, M87, M89 or M118, especially *S. pyogenes* SF370.

An "effective amount" of a pharmaceutical peptide, a pharmaceutical nucleic acid or an antibody of the invention may be calculated as that amount capable of exhibiting an *in vivo* effect, e.g. preventing or ameliorating a sign or symptom of infection, particularly *S. pyogenes* infection, especially of *S. pyogenes* serotype M1, M2, M3, M4, M5, M6, M11, M12, M14, M19, M22, M24, M25, M28, M44, M49, M57, M59, M60, M61, M76, M83, M84, M87, M89 or M118, especially *S. pyogenes* SF370. Such amounts may be determined by one of skill in the art. Preferably, such a composition is administered parenterally, preferably intramuscularly or subcutaneously. However, it may also be formulated to be administered by any other suitable route, including orally or topically. The selection of the route of delivery and dosage of such therapeutic compositions is within the skill of the art.

Treatment in the context of the present invention refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented.

Another subject of the invention relates to a method of diagnosing a *S. pyogenes* infection comprising the steps of:

(a) contacting a sample obtained from a subject with the peptide according to the invention; and

(b) detecting the presence of an antibody against *S. pyogenes* in the sample.

The peptides of the invention may be used for the detection of the *S. pyogenes*, particularly *S. pyogenes* serotype M1, M2, M3, M4, M5, M6, M11, M12, M14, M19, M22, M24, M25, M28, M44, M49, M57, M59, M60, M61, M76, M83, M84, M87, M89 or M118, especially *S. pyogenes* SF370. Preferably such detection is for diagnosis, more preferable for the diagnosis of a disease, most preferably for the diagnosis of a *S. pyogenes* infection. The

peptides or polypeptides may be used to detect the presence of a *S. pyogenes*-specific antibody or fragment thereof e.g. in a sample obtained from a subject. The sample may be e.g. a blood sample. Alternatively, the presence of a *S. pyogenes*-specific antigen can be detected using an antibody of the invention.

Accordingly, an alternative method of diagnosing a *S. pyogenes* infection comprises the steps of:

(a) contacting a sample obtained from a subject with the antibody according to the invention; and

(b) detecting the presence of an antigen of *S. pyogenes* in the sample.

The present invention also relates to diagnostic assays such as quantitative and diagnostic assays for detecting levels of the peptides or antibodies of the present invention in cells and tissues or body fluids, including determination of normal and abnormal levels. Assay techniques that can be used to determine levels of a peptide or an antibody, in a sample derived from a host are well known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis and ELISA assays. Among these, ELISAs frequently are preferred. An ELISA assay initially comprises preparing an antibody specific to the peptide, particularly the antigen, preferably a monoclonal antibody. In addition, a reporter antibody generally is prepared which binds to the monoclonal antibody. The reporter antibody is attached to a detectable reagent such as radioactive, fluorescent or enzymatic reagent, such as horseradish peroxidase enzyme.

The peptides or antibodies of the present invention may also be used for the purpose of or in connection with an array. More particularly, at least one of the peptides or antibodies of the present invention may be immobilized on a support. Said support typically comprises a variety of antigens and fragments thereof whereby the variety may be created by using one or several of the peptides or antibodies of the present invention. The characterizing feature of such array as well as of any array in general is the fact that at a distinct or predefined region or position on said support or a surface thereof, a distinct polypeptide is immobilized. Because of this any activity at a distinct position or region of an array can be correlated with a specific polypeptide. The number of different peptides or antibodies of

the present invention immobilized on a support may range from as little as 10 to several 1000 different peptides or antibodies of the present invention.

The manufacture of such arrays is known to the one skilled in the art and, for example, described in US patent 5,744,309. The array preferably comprises a planar, porous or non-porous solid support having at least a first surface. Preferred support materials are, among others, glass or cellulose. It is also within the present invention that the array is used for any of the diagnostic applications described herein. Apart from the peptides or antibodies of the present invention also the nucleic acid molecules according to the present invention may be used for the generation of an array as described above.

Another aspect of the invention relates to a method for identifying a ligand capable of binding to a peptide according to the invention comprising:

(a) providing a test system comprising the peptide,

(b) contacting the test system with a test compound, and

(c) detecting a signal generated in response to the binding of the test compound to the peptide.

More particularly, the method may be carried out by contacting an isolated or immobilized peptide according to the invention with a candidate ligand under conditions to permit binding of the candidate ligand to the peptide, wherein the test system comprises a component capable of providing a detectable signal in response to the binding of the candidate ligand to said peptide; and detecting the presence or absence of a signal generated in response to the binding of the ligand to the peptide. The ligand may be an agonist or an antagonist.

Test systems for detection binding of a ligand are known to the skilled artisan and include e.g. binding assays with labeled ligand such as radioligands, fluorescence-labeled ligands or enzyme-labeled ligands.

The test compound can be any test compound either naturally occurring or chemically synthesized. Naturally occurring test compounds include in particular antibodies, preferably those showing similarity to the antibodies of the invention. In one preferred

embodiment of the invention the test compound is provided in the form of a chemical compound library. Chemical compound libraries include a plurality of chemical compounds and have been assembled from any of multiple sources, including chemically synthesized molecules and natural products, or have been generated by combinatorial chemistry techniques. They are especially suitable for high throughput screening. They may be comprised of chemical compounds of a particular structure or compounds of a particular creature such as a plant.

The method for identifying a ligand may also include the following steps:

(a) providing a peptide according to the invention,

(b) providing an interaction partner to the peptide especially an antibody according to the invention,

(c) allowing interaction of the peptide to said interaction partner to form a interaction complex,

(d) providing a test compound,

(e) allowing a competition reaction to occur between the test compound and the interaction complex, and

(f) determining whether the test compound inhibits or reduces the interaction activities of the peptide with the interaction partner.

The ligands identified may be employed, for instance, to inhibit diseases arising from infection with Streptococcus, especially *S. pyogenes* and may therefore be formulated in a pharmaceutical composition.

In a last aspect, the peptide according to the invention is used for the isolation and/or purification and/or identification of a ligand of the peptide, wherein the isolation and/or purification and/or identification of the ligand may be carried out as detailed above or as known to the person skilled in the art. In a preferred embodiment of the invention an affinity device may be used. The affinity device may comprise as least a support material and any peptide according to the present invention, which is attached to the support material. Because of the specificity of the peptides according to the present invention for their target cells or target molecules or their interaction partners, the peptides allow a selective removal of their interaction partner(s) from any kind of sample applied to the

support material provided that the conditions for binding are met. The sample may be a biological or medical sample, including but not limited to, fermentation broth, cell debris, cell preparation, tissue preparation, organ preparation, blood, urine, lymph liquid, liquor and the like. The peptide may be attached to the matrix in a covalent or non-covalent manner. Suitable support material is known to the one skilled in the art and can be selected from the group comprising cellulose, silicon, glass, aluminium, paramagnetic beads, starch and dextrane.

The present invention is further illustrated by the following figures, examples and the sequence data, from which further features, embodiments and advantages may be taken. It is to be understood that the present examples are given by way of illustration only and not by way of limitation of the disclosure.

Figure 1 shows the protection achieved by active immunization with selected *S. pyogenes* antigens and sub-constructs in a mouse lethality model.

Figure 2 shows the protection achieved by active immunization with selected *S. pyogenes* antigens and sub-constructs in a mouse lethality model.

Figure 3 shows the protection achieved by active immunization with selected *S. pyogenes* antigens and sub-constructs in a mouse lethality model.

Figure 4 shows the protection achieved by active immunization with selected *S. pyogenes* antigens in a mouse lethality model.

Table 1 shows the recombinant proteins of *S. pyogenes* and fragments thereof assessed for protection in murine models of infection.

Table 2 shows the oligonucleotides used for the cloning of genes encoding antigenic proteins and fragments thereof of *S. pyogenes.*

Table 3 shows the *S. pyogenes* strains used for the gene conservation study.

Table 4 shows the oligonucleotides used for PCR and sequencing of the *S. pyogenes* genes.

Table 5 shows the variable amino acid positions of Spy0269 from *S. pyogenes* strains.

Table 6 shows the variable amino acid positions of Spy0292 from *S. pyogenes* strains.

Table 7 shows the variable amino acid positions of Spy0416 from *S. pyogenes* strains.

Table 8 shows the variable amino acid positions of Spy0488 from *S. pyogenes* strains.

Table 9 shows the variable amino acid positions of Spy0872 from *S. pyogenes* strains.

Table 10 shows the variable amino acid positions of Spy0895 from *S. pyogenes* strains.

Table 11 shows the variable amino acid positions of Spy1536 from *S. pyogenes* strains.

Table 12 shows the variable amino acid positions of Spy1666 from *S. pyogenes* strains.

FIGURES

Figure 1: Protection achieved by active immunization with selected *S. pyogenes* antigens and sub-constructs in a mouse lethality model. CD-1 mice (10 mice per group) were immunized subcutaneously with recombinant antigens cloned from an emm type 1 *S. pyogenes* strain (SF370) and challenged with the MA-A20 (emm type 23) strain. Survival was monitored for 14 days post-challenge. Mice were immunized subcutaneously with 50 µg recombinant protein adjuvanted with CFA/IFA. **(A)** Spy0292, and its sub-constructs Spy0292-1 and Spy0292-3; Spy0488; **(B)** Spy0872 and its sub-construct Spy0872-2. Anesthetized mice were challenged intranasally with 10^8 cfu *S. pyogenes* MA-A20. Adjuvant control mice were used as negative controls, while M1 (Spy2018) served as positive control. Numbers of surviving mice are plotted as percentage of total mice.

Figure 2: Protection achieved by active immunization with selected *S. pyogenes* antigens and sub-constructs in a mouse lethality model. CD-1 mice (10 mice per group) were immunized subcutaneously with recombinant antigens cloned from an emm type 1 *S. pyogenes* strain (SF370) and challenged with the MA-A20 (emm type 23) strain. Survival was monitored for 14 days post-challenge. Mice were immunized subcutaneously with 50 µg recombinant protein adjuvanted with CFA/IFA. **(A)** Spy0269 and its sub-construct Spy0269-1; **(B)** Spy0416A and 3 sub-constructs (Spy0416A-1, Spy0416A-6 and Spy0416A-7) and Spy0416B. Anesthetized mice were challenged intranasally with 10^8 cfu *S. pyogenes* MA-A20. Adjuvant control mice were used as negative controls, while M1 protein (Spy2018) served as positive control. Numbers of surviving mice are plotted as percentage of total mice.

Figure 3: Protection achieved by active immunization with selected *S. pyogenes* antigens or sub-constructs in a mouse lethality model. CD-1 mice (10 mice per group) were immunized subcutaneously with recombinant antigens cloned from an emm type 1 *S. pyogenes* strain (SF370) and challenged with the MA-A20 (emm type 23) strain. Survival was monitored for 14 days post-challenge. Mice were immunized subcutaneously with 50 µg recombinant protein adjuvanted with aluminum hydroxide. **(A)** Spy1727, Spy0269-1, Spy0872-2, and Spy0416A-1; **(B)** Spy1666, Spy1536, Spy0895, and Spy0292-1. Anesthetized mice were challenged intranasally with 10^8 cfu *S. pyogenes* MA-A20. Adjuvant control mice were used as negative controls, while M1 protein (Spy2018) served as positive control. Numbers of surviving mice are plotted as percentage of total mice.

Figure 4: Protection achieved by active immunization with selected *S. pyogenes* antigens in a mouse lethality model. BALB/c mice (10 mice per group) were immunized intranasally with recombinant antigens cloned from an emm type 1 *S. pyogenes* strain (SF370) and challenged either with **(A)** MA-A20 (emm type 23) strain or with **(B)** MA-A147 (emm type 11/106) strain. Survival was monitored for 14 days post-challenge. Mice were immunized intranasally with 30-50 µg recombinant protein adjuvanted with IC31™. **(A)** Spy1536 and Spy0895; **(B)** Spy1727 and Spy1536. Anesthetized mice were challenged intranasally with 10^6 cfu *S. pyogenes* MA-A20 or 10^8 cfu *S. pyogenes* MA-A147. Adjuvant control mice were used as negative controls, while M1 protein (Spy2018) served as positive control. Numbers of surviving mice are plotted as percentage of total mice.

EXAMPLES

Example 1: Group A streptococcal antigens and fragments thereof inducing protective immune responses against lethal sepsis in intranasal challenge models.

Experimental procedures

Cloning and expression of recombinant pneumococcal proteins

Cloning of genes / DNA fragments:

The gene/DNA fragment of interest (see Table 1) was amplified from genomic DNA of *Streptococcus pyogenes* SF370 (serotype M1) by PCR using gene specific primers (see Table 2). Apart from the gene specific part, the primers had restriction sites that aided in a directional cloning of the amplified PCR product. The gene annealing (specific) part of the primer ranged between 15-30 bases in length. The PCR products obtained were digested with the appropriate restriction enzymes and cloned into the pET28b (+) vector (Novagen) for His-tagged proteins. The constructs including full length and fragments of the selected antigens are listed in Table 1. Once the recombinant plasmid was confirmed to contain the gene of interest, *E. coli* BL21 star® cells (Invitrogen) that served as expression host were transformed.

Expression and purification of proteins:

E coli BL21 star® cells harboring the recombinant plasmid were grown into log phase in the required culture volume. Once an OD_{600nm} of 0.6 was reached the culture was induced with 0.5 mM IPTG (isopropyl-beta-D-thiogalactopyranoside) at 37°C for 3 hours. The cells were harvested by centrifugation, lysed by a combination of the freeze-thaw method followed by disruption of cells with BugBuster® (Novagen). The lysate was separated by centrifugation into soluble (supernatant) and insoluble (pellet) fractions. Depending on the location of the protein different purification strategies were applied.

A) If the His-tagged protein was in the soluble fraction, protein purification was done by binding the supernatant to Ni-Sepharose beads (Ni-Sepharose™ 6 Fast Flow, GE Healthcare). Due to the presence of the hexa Histidine (6xHIS) at the C terminus of the

expressed protein, it bound to the Ni-Sepharose while the other contaminating proteins were washed from the column by wash buffer. The protein was eluted by 500 mM Imidazole in 20 mM NaH_2PO_4, 0.5 mM NaCl buffer at pH 7.4. The eluate was concentrated, assayed by Bradford for protein concentration and checked by SDS-PAGE and Western blot.

B) If the protein was present in the insoluble fraction the pellet was solubilized in suitable buffer containing 8 M urea and applied onto the Ni-NTA column under denaturing conditions (in buffer containing 8 M urea) using the same materials and procedure as mentioned above. Contaminating proteins were washed from the column by wash buffer without urea. Refolding of the His-tagged protein was performed while the protein was immobilized on the Ni-NTA matrix. After renaturation, proteins were eluted by the addition of 500 mM Imidazole. The eluate was dialyzed to remove traces of urea and concentrated if the volume was large, checked by SDS-PAGE and measured by the Bradford method.

Animal protection studies

Animals:

CD-1 or BALB/c female mice (6 – 8 weeks) were used.

Active immunization (subcutaneous route):

50 µg of recombinant proteins buffered in PBS were injected subcutaneously into CD-1 mice (volume 100 µL), adjuvanted with Complete Freund adjuvant (CFA, final concentration: 50%), aluminium hydroxide (ALUM, final concentration: 1%) or IC31™ (final concentration: 100 nmol L-KLKLLLLLKLK (SEQ ID NO: 55), 4 nmol oligodexoynucleotide ODN1a $(dIdC)_{13}$ in PBS) (Intercell AG, Vienna, Austria). Animals were boosted twice with the same amount of protein and adjuvant (except for CFA where Incomplete Freund adjuvant (IFA) was used for the booster immunizations; final concentration: 50%), at days 14 and 28. The published (Dale et al., J. Immunol. 151: 2188 (1993)) protective M1 or M23 protein antigens were used as positive controls, while mice immunized with adjuvant only served as negative controls. Antibody titers were measured at day 35 by ELISA using the respective recombinant proteins.

Active immunization (intranasal route):

30 - 50 µg of recombinant proteins buffered in PBS were injected intranasally into BALB/c mice (volume 20 µL), adjuvanted with IC31™ (final concentration: 10 nmol L-KLKLLLLLKLK (SEQ ID NO: 55), 0.4 nmol oligodexoynucleotide ODN1a $(dIdC)_{13}$ in PBS) (Intercell AG, Vienna, Austria). Animals were boosted three times with the same amount of protein and adjuvant at days 7, 14 and 28. The published protective M1 or M23 protein antigens were used as positive controls, while mice immunized with adjuvant only served as negative controls. Antibody titers were measured at day 35 by ELISA using the respective recombinant proteins.

Bacterial challenge:

Freshly grown *S. pyogenes* strains MA-A20 or MA-A147 were used. 1 mL bacterial suspension from an o/n culture of the respective *S. pyogenes* strain was added to 50 mL THY culture medium. Optical density was measured until the bacterial suspension reached an OD_{600nm} between 0.4 and 0.6. Bacterial counts were determined using an individually established growth curve. Bacterial cells were spun down and adjusted with PBS to obtain the desired cfu count. In order to determine the viable cell numbers present in the bacterial inoculum, cfus were determined via plating on blood agar plates. 10^6 - 10^8 cfus were applied intranasally (20 µL) into individually anesthetized mice. Protection by immunization was measured by a bacteraemia / sepsis model where survival rates were followed for 2 to 3 weeks post-challenge and survival was expressed in percentage of the total number of animals (10 mice / group).

Results

Group A streptococcal antigens and/or their fragments were identified showing protection in an intranasal mouse sepsis/lethality model. As the target indication for a preventive vaccine in humans is pharyngitis, an intranasal challenge model for the evaluation of candidate antigens is believed to be physiologically more relevant than an intravenous or intraperitoneal model, which have been described previously (Guzman et al., J. Inf. Dis. 179: 901 (1999); Stalhammar-Carlemalm et al., Mol. Microbiol. 33: 208 (1999)). Therefore protection was assessed in three distinct models, all applying the bacterial

challenge via the intranasal route. Protection was observed for 9 distinct proteins in the intranasal challenge model, some of which were tested as a fragment of the full length recombinant protein.

Since protection against streptococcal challenge is mediated by antibodies, immunizations were first performed using CFA/IFA as adjuvant in order to obtain very high levels of antibodies. Subsequently, experiments were also performed with Alum and IC31™ as adjuvants, as these adjuvants are suited for use in humans and would be a preferred choice for a vaccine to prevent group A streptococcal infections in humans. As can be seen for the experiment depicted in Figure 1, fragment Spy0292-1 performed as well as full length Spy0292 protein for protection, while Spy0292-3 showed lower levels of protection. This clearly indicates that one region useful for protection lies within the sequence encompassing the Spy0292-1 protein.

Similar results were obtained for the proteins, Spy0269 (good protection also observed with Spy0269-1), Spy0416 (good protection also observed with Spy0416A-1, Spy0416A-6 and Spy0416A-7), and Spy0872 (good protection also observed with Spy0872-2).

For the proteins Spy0488, Spy0895, and Spy1727 full length recombinant proteins were used (Table 1), as these proteins have been shown for the first time to be capable to provide protection against lethal *S. pyogenes* challenge. Especially protein Spy0895 shows promise as a vaccine candidate, because it provided protection against group A streptococcal infection in all three models listed in Table 1.

Spy1536 and Spy1666 have been shown to provide protection in an intravenous challenge model before (WO 2004/078907), but importantly it could now be shown that they also provide protection in the physiologically more relevant intranasal challenge model. Spy1536 was most consistent in providing significant protection in all three models of GAS infection. Besides these two antigens, Spy0895 and Spy1536, several antigens showed protection in at least 2 models: Spy0269-1, Spy0292-1, Spy0416A-1, Spy0872-2, Spy1666 and Spy1727. Importantly, several antigens showed a level of protection that was as high as the level seen for the positive control protein M1 (e.g. Spy0416A-1, Spy0488, Spy0895; Table 1).

These data clearly provide evidence, that the selected proteins are promising candidates for vaccine development. In addition, proteins Spy0269, Spy0292, Spy0416, and Spy0872 have been shown to possess amino acid sequences that are dispensable for protection, since sub-fragments were capable to provide the same or even superior levels of protection than the full length recombinant protein.

Table 1: Recombinant proteins of *S. pyogenes* and fragments thereof assessed for protection in murine models of infection.

ORF/ Protein	Length[1] (aa)	Amino acids[1] (from – to)	SEQ ID No	Calculated MW (kDa)[2]	Vector	Base pairs[1] (from – to)	Protection[3]
Spy0269	837	36 - 873	57	92.34	pET28b	106-2619	10% (30%, 60%)[A]
Spy0269-1	*452*	37-488	1	50.85	pET28b	*109-1464*	50% (10%, 50%)[B,A,C]
Spy0292	*388*	23 - 410	68	44.91	pET28b	*67-1233*	60% (10%, 90%)[A,C]
Spy0292-1	*162*	23-184	2	19.41	pET28b	*67-554*	56% (10%, 90%)[A,B]
Spy0292-3	278	23-300	3	32.39	pET28b	67-900	30% (10%, 90%)[A]
Spy0416A	*834*	34 - 867	89	95.80	pET28b	*100-2601*	20% (10%, 63%)[A]
Spy0416A-1	*644*	34-677	4	74.70	pET28b	*100-2031*	80% (20%, 80%)[C,A]
Spy0416A-6	*311*	148-458	5	38.77	pET28b	*442-1374*	40% (10%, 63%)[A]
Spy0416A-7	*487*	72-558	6	57.68	pET28b	*214-1674*	63% (10%, 63%)[A]
Spy0416B	882	736 - 1617	56	103.08	pET28b	2206-4851	20% (10%, 63%)[A]
Spy0488	*331*	1-331	8	37.84	pET28b	*1-993*	90% (20%, 80)[C,A]
Spy0872	*613*	28 - 640	120	68.38	pET28b	82-1920	20% (0%, 60%)[A]
Spy0872-2	290	351-640	7	33.02	pET28b	1051-1920	60% (0%, 60%)[A,C,B]
Spy0895	261	2-262	9	32.15	pET28b	4-786	90% (20%, 80%)[C,A,B]
Spy1536	314	32-345	131	35.27	pET28b	94-1035	70% (20%, 80%)[C,A,B]
Spy1666	315	23-337	132	37.02	pET28b	67-1011	60% (20%, 80%)[C,B]
Spy1727	263	1-263	10	32.43	pET28b	1-789	70% (20%, 80%)[C,B]

1 Length, amino acids and base pairs are calculated for the *S. pyogenes* gene specific sequence only.

2 The calculated molecular weight includes amino acids derived from the vector and the His6-tag.

3 Protection is based on the animal model as indicated:

A s.c. immunization using CFA/IFA as adjuvant, i.n. challenge with *S. pyogenes* A20

B s.c. immunization using ALUM as adjuvant and i.n. challenge with *S. pyogenes* A20

C intranasal immunization using IC31™ or a mucosal adjuvant and intranasal challenge with either *S. pyogenes* A20 or A147.

Brackets show protection in the respective model with the negative (PBS + adjuvant only) and positive control (M protein). If protection was seen in more than one model, the protection data of the model listed first are shown.

Table 2: Oligonucleotides used for the cloning of genes encoding antigenic proteins and fragments thereof of *S. pyogenes*.

ORF-protein	Plasmid name	Primer [1]	Name	Restriction enzyme
SPy0269	pET28b-SPy0269	TAGTAGCCATGGGCGATGATAGAGCCTCA GGA SEQ ID NO: 21	210-2129	NcoI
		TAGTAGGCGGCCGCCTTAGATTCCTTACG GAACCT SEQ ID NO: 22	210-2196	NotI
SPy0269-1	pET28b-SPy0269-1	TAGTAGCCATGGGCGATGATAGAGCCTCA GGA SEQ ID NO: 23	210-2129	NcoI
		TAGTAGGCGGCCGCAACAGGCGCATTAGG G SEQ ID NO: 24	210-2719	NotI
SPy0292	pET28b-SPy0292	TAGTAGCCATGGGCGAAGAGTATTCGGTA ACTGC SEQ ID NO: 25	210-2131	NcoI
		TAGTAGGCGGCCGCTAAAGAGGTATTGAC ATACCT SEQ ID NO: 26	210-2197	NotI
SPy0292-1	pET28b-SPy0292-1	TAGTAGCCATGGGCGAAGAGTATTCGGTA ACTGC SEQ ID NO: 27	210-2131	NcoI
		TAGTAGGCGGCCGCGCAAAAACAATTTTC ATCATC SEQ ID NO: 28	210-2954	NotI
SPy0292-3	pET28b-SPy0292-3	TAGTAGCCATGGGCGAAGAGTATTCGGTA ACTGC SEQ ID NO: 29	210-2131	NcoI
		TAGTAGGCGGCCGCTTCAATTAACTGGAC TTTTTG SEQ ID NO: 30	210-2956	NotI
SPy0416A	pET28b-SPy0416A	TAGTAGGAATTCGGCAGATGAGCTAAGCA CAATG SEQ ID NO: 31	210-2246	EcoRI
		TAGTAGCTCGAGCTCTGAACCAAGAGTGA CAAG SEQ ID NO: 32	210-2247	XhoI
SPy0416A-1	pET28b-SPy0416A-1	TAGTAGGAATTCGGCAGATGAGCTAAGCA CAATG SEQ ID NO: 33	210-2246	EcoRI
		TAGTAGCTCGAGTGCCCCTTGCTGACGCG GTG SEQ ID NO: 34	210-2663	XhoI
SPy0416A-6	pET28b-SPy0416A-6	TAGTAGGAATTCGGCAGTTATTGACACAGG G SEQ ID NO: 35	210-2715	EcoRI
		TAGTAGCTCGAGTAGGCTATCTTTTATGTC SEQ ID NO: 36	210-2717	XhoI
SPy0416A-7	pET28b-SPy0416A-7	TAGTAGGAATTCGTCACAAATCACTCTCAA G SEQ ID NO: 37	210-2716	EcoRI
		TAGTAGCTCGAGACTTCCTGTACCATTGCC SEQ ID NO: 38	210-2718	XhoI
SPy0416B	pET28b-SPy0416B	TAGTAGGAATTCGCATGTAGACCCACAAA AGGGC SEQ ID NO: 39	210-2248	EcoRI
		TAGTAGCTCGAGCGTTGATGGTAGGGCTTT TGC SEQ ID NO: 40	210-2249	XhoI
SPy0488	pET28b-SPy0488	TAGTAGCCATGGGCTTGCGGCAGATTCAG TCCATT SEQ ID NO: 41	210-2139	NcoI
		TAGTAGGCGGCCGCACTTTTTAACCTGTCC TCAGC SEQ ID NO: 42	210-2199	NotI
SPy0872	pET28b-SPy0872	TAGTAGCCATGGGCGATCAAGTTGATGTG CAATTC SEQ ID NO: 43	210-2143	NcoI
		TAGTAGGCGGCCGCTGTTATTGGAAGAGT GGAACT SEQ ID NO: 44	210-2144	NotI
SPy0872-2	pET28b-SPy0872-2	TAGTAGCCATGGGCGCTATAATAAATCATG CT SEQ ID NO: 45	210-2962	NcoI
		TAGTAGGCGGCCGCTGTTATTGGAAGAGT GGAACT SEQ ID NO: 46	210-2144	NotI
SPy0895	pET28b-SPy0895	TAGTAGCCATGGGCACTAATAATCAAACA	210-2145	NcoI

ORF-protein	Plasmid name	Primer [1]	Name	Restriction enzyme
		CTA SEQ ID NO: 47 TAGTAGGCGGCCGC**GACAATAGATTGTCT** **CCAAAG** SEQ ID NO: 48	210-2201	NotI
SPy1536	pET28b-SPy1536	TAGTAGCCATGG**GCATTGAAATGCCTGGA** **GGCG** SEQ ID NO: 49	210-2161	NcoI
		TAGTAGGCGGCCGC**TTTGCGAAGATAAAC** **CAGTGC** SEQ ID NO: 50	210-2207	NotI
SPy1666	pET28b-SPy1666	TAGTAGCCATGG**GCACAAAAGAATTTCATC** **ACGTG** SEQ ID NO: 51	210-2165	NcoI
		TAGTAGGCGGCCGC**TTTCCGAATTTTTTTG** **GCAAC** SEQ ID NO: 52	210-2209	NotI
SPy1727	pET28b-SPy1727	TAGTAGCCATGG**GCGTGACAACGACGGAA** **CAAG** SEQ ID NO: 53	210-2167	NcoI
		TAGTAGGCGGCCGC**TTTCTTTCTAAATATT** **TCTCT** SEQ ID NO: 54	210-2210	NotI

[1] Primer, letters in bold indicate gene-specific sequences, letters underlined indicate the restriction enzyme sites, letters in normal font indicate sequences necessary for cloning, but not present in the final plasmid construct used for expression. The first primer always refers to the sense and the second primer to the anti-sense oligonucleotide in relation to the encoded gene used for amplification.

Example 2: Group A streptococcal antigens and variants thereof.

Experimental procedures

Preparation of streptococcal genomic DNA

5 mL Todd-Hewitt Broth medium were inoculated with the respective strain of *S. pyogenes* (as listed in Table 3) from a frozen stab and grown without shaking at 37°C overnight. 4 mL of the culture were then harvested by centrifuging at 13,000 rpm in a biofuge fresco (Haereus) for 5 min and the supernatant was removed. DNA was isolated from the bacterial cell pellets following the protocol of Wizard® Genomic DNA Purification Kit (Promega). The DNA pellets were finally dried on air and dissolved in 70 µl ddH_2O.

PCR and sequence analyses of S. pyogenes genes

In order to determine the sequence of an antigen from diverse *S. pyogenes* strains, PCR was performed with primers specific for the gene of interest. *S. pyogenes* strains used for these analyses are shown in Table 3. Oligonucleotide sequences as primers for PCR were designed for the selected antigens in order to be able to amplify the full gene. Sequencing was performed with dedicated primers using the PCR products as templates. The sequences of the oligonucleotides are listed in Table 4. Genomic DNA of all *S. pyogenes*

strains was prepared as described above. PCR was performed in a reaction volume of 25 µl using Taq polymerase (1 U), 200 nM dNTPs, 10 pMol of each oligonucleotide and the kit according to the manufacturer's instructions (Invitrogen, The Netherlands). As standard, 30 cycles (1x: 5 min. 95°C, 30x: 30 sec. 95°C, 30 sec. 56°C, 120 sec. 72°C, 1x 4 min. 72°C) were performed, unless conditions had to be adapted for individual primer pairs. PCR samples were sequenced with the oligonucleotides as listed in Table 10. Sequencing was performed at Agowa (Germany).

Table 3: *S. pyogenes* clinical isolates utilized for the present study.

No.	Strain	Country of origin	Serotype
1	Schmitz 1/94	Netherlands	1
2	Schmitz 1/12	Portugal	1
3	Schmitz 1/5	Portugal	1
4	Schmitz 2/14	Germany	1
5	Schmitz 1/74	England	3
6	Schmitz 1/35	Spain	3
7	Schmitz 1/41	France	3
8	RDN 78	unknown	3.1
9	Schmitz 1/17	Portugal	4
10	Schmitz 1/156	Switzerland	4
11	Schmitz 1/22	Spain	4
12	RDN 60	unknown	5
13	Schmitz 1/174	Austria	6
14	Schmitz 1/97	Belgium	6
15	Schmitz 1/29	Spain	9
16	Schmitz 1/92	Netherlands	11
17	Schmitz 1/39	Spain	12
18	Schmitz 1/248	Poland	12
19	Schmitz 1/59	England	12
20	RDN 02	unknown	19
21	Schmitz 1/76	England	22
22	Schmitz 1/177	Austria	22
23	Schmitz 1/43	France	22
24	Schmitz 2/32	Germany	22
25	RDN 136	unknown	22.2
26	Schmitz 1/136	Germany	25
27	Schmitz 1/56	France	28
28	Schmitz 1/108	Belgium	28
29	Schmitz 1/85	Netherlands	28
30	Schmitz 2/50	Germany	28
31	Schmitz 1/194	Italy	44
32	Schmitz 1/234	Turkey	44
33	Schmitz 1/103	Belgium	44
34	Schmitz 1/253	Poland	49
35	Schmitz 1/141	Germany	49
36	Schmitz 1/123	Germany	49

37	Schmitz 2/30	Germany	66 or 90
38	Schmitz 1/144	Germany	76
39	Schmitz 1/99	Belgium	78
40	RDN 120	unknown	81
41	Schmitz 1/142	Germany	83
42	Schmitz 1/176	Austria	83
43	Schmitz 1/25	Spain	83
44	RDN 75	unknown	85
45	Schmitz 2/46	Germany	89
46	Schmitz 2/9	Germany	90
47	Schmitz 2/23	Germany	90
48	RDN 116	unknown	94
49	Schmitz 1/55	France	118
50	Schmitz 1/68	England	118
51	Schmitz 1/3	Portugal	118

Table 4: Oligonucleotides used for sequence conservation analyses. Shown are the ORF and primer names, orientation of the primer relative to the gene, the sequence, and the position relative to the gene. Oligonucleotides were used for both PCR amplification of the gene or gene fragment and subsequent sequence analyses.

ORF	Primer name	Orientation	Sequence	SEQ ID NO:	Position relative to gene
Spy0269	210-4752	sense	TGACCTTCAAATCATTGCTGA	209	-103 to -82
	210-4759	antisense	TTTTGCACTTCTGGTGTCAA	210	1014 to 1034
	210-4754	sense	TTGCCAAAGCTAGTCCAGGT	211	931 to 951
	210-4761	antisense	AGTATTATCAATGCGCTCACG	212	2028 to 2049
	210-4756	sense	AAAAGCTCATTTGCAATATCTAAGG	213	1967 to 1992
	210-4763	antisense	GCTGGTGAATCTGATTTTTCAA	214	2875 to 2897
Spy0292	210-4575	sense	TCTTGTGAGGTAAGTCATTACCTTAG	215	-79 to -53
	210-4576	antisense	TTCATCATCTGGTTCTGTATTAGG	216	516 to 540
	210-4577	sense	GGTCGTCAATTCAACTGGC	217	464 to 483
	210-4578	antisense	GCGATCATTGTGGATGATTTC	218	1031 to 1052
	210-4579	sense	AAACTGTCAAACTTGTAGCCC	219	946 to 967
	210-4580	antisense	TGTTAGGATTGGCCTAGTTTG	220	1304 to 1325
Spy0416	210-4588	sense	TGAGTTAATGATTAACATTAAACTGGT	221	-56 to -29
	210-4591	antisense	TGACATAAGCAAATTGATGCG	222	1387 to 1408
	210-4592	sense	CCATCTATTCAGAGTCTGTCGAC	223	1327 to 1350
	210-4595	antisense	CCTTGTCACTAGCATGGTAGAC	224	2802 to 2824
	210-4596	sense	TTGCAGCCTTCAAAGGTG	225	2749 to 2767
	210-4599	antisense	AAGACACATTACCAGCTCTATCTTC	226	4128 to 4153
	210-4600	sense	CAGATGGTTCTTACACCATTTC	227	4063 to 4085
	210-4603	antisense	AATCTCAAAGAAAGGTCAGACTG	228	4982 to 5005
Spy0488	210-5497	sense	AAAGCTCGTCATTTTATATGATTT	229	-195 to -171
	210-4767	antisense	TTTAATGAGAGTTGTCATTCGTTCA	230	497 to 522
	210-4765	sense	TTTTCTTGTTCAACCGCAAG	231	404 to 424
	210-4766	antisense	GCGCTCACAGCTACTTCAGA	232	1052 to 1072
Spy0872	210-4581	sense	CAAAATCATAGTAAACTTGATCTATAACG	233	-55 to -26
	210-4584	antisense	GAAGAATTAGTTGCAGTTCCG	234	1103 to 1124
	210-4585	sense	GTTGCTGTAGCACCAGGTATC	235	1005 to 1026

	210-4587	antisense	CCAGCACGAATTAGATCATCTAG	236	2111 to 2134
Spy0985	210-4768	sense	CTGAAGAGCGCCAAACAACT	237	-63 to -43
	210-4771	antisense	TCGAAGAAGTAACCTTTGATTAATGT	238	864 to 890
Spy1536	210-4772	sense	GCTCTAGTCGTGTGAGAGAGCTAA	239	-90 to -66
	210-4775	antisense	TGTCTATCTGGTTCAACCGTTTT	240	1089 to 1112
Spy1666	210-4780	sense	GTGGCTAAGTCAGTGCTTGCT	241	-80 to -59
	210-4783	antisense	AAGTTTTTATTCGTTTTTGCAAGG	242	1055 to 1079
Spy1727	210-4776	sense	GATCATTGACTAAGTAGCCTAAAACAA	243	-76 to -49
	210-4779	antisense	CCAAAAACGTCATGCCAAC	244	879 to 898

RESULTS

Gene conservation analysis of selected streptococcal antigens

The PCR and sequencing of the 9 selected genes was performed as described under Methods. Table 3 shows the strains used for sequencing, while Table 4 lists the oligonucleotides employed for the PCR and sequencing analyses.

Sequence analyses of Spy0269

Sequences were obtained from all 51 strains. The level of amino acid sequence identity ranged from 98.7% to 100% as compared to the sequence of Spy0269 from *S. pyogenes* SF370. Table 5 lists all 36 amino acid positions which showed a distinct amino acid as compared to Spy0269 from *S. pyogenes* SF370.

Table 5: Gene conservation of Spy0269. [1], observed amino acid at respective position in any of the sequenced genes of the respective *S. pyogenes* strains.

Position in SF370 gene	Alignment position	Amino acid in SF370 gene	AA change[1]	AA change[2]	Strains with the respective change[1]	Strains with the respective change[2]
30	30	V	I		Schm1_142, Schm1_177, Schm1_43, RDN75	
68	68	D	E		Schm1_76, Schm1_92, Schm1_142, Schm1_176, Schm1_177, Schm1_25, Schm1_43, Schm2_32, RDN136, RDN75	
73	73	T	A		Schm1_142, Schm1_177, Schm1_43	

80	80	E	K		Schm1_55, Schm1_68, Schm1_3, Schm2_23, Schm2_30	
83	83	E	K		Schm1_17, Schm1_59, Schm1_97	
94	94	E	K		Schm1_142, Schm1_177, Schm1_43	
97	97	H	N		Schm1_99, Schm2_14, Schm2_46	
150	150	A	V		Schm1_74, Schm1_35, Schm1_141, Schm1_174, Schm1_41, Schm2_9, Schm2_50, RDN60, RDN78, RDN75	
230	230	A	G		Schm1_35	
249	249	E	D		Schm1_103	
276	276	A	V		Schm1_56, Schm1_108	
279	279	G	D		Schm1_55, Schm1_68, Schm1_3, Schm2_23, Schm2_30	
307	307	A	G		Schm1_92	
482	482	H	R		Schm1_17, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_253, Schm1_108, Schm1_141, Schm1_174, Schm1_176, Schm1_177, Schm1_25, Schm1_43, Schm1_59, Schm1_97, Schm1_99, Schm1_123, Schm1_136, Schm2_14, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN120, RDN116	
485	485	N	K		Schm1_39, Schm1_55, Schm1_68, Schm1_156, Schm1_248, Schm1_3,	

					Schm1_22, Schm1_29, Schm2_23, Schm2_30, RDN75	
537	537	G	S		Schm1_76, Schm1_92, Schm1_142, Schm1_176, Schm1_177, Schm1_25, Schm1_43, Schm2_32, RDN136	
577	577	Q	E		Schm1_39, Schm1_76, Schm1_92, Schm1_142, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_248, Schm1_22, Schm1_25, Schm1_29, Schm1_43, Schm2_32, Schm2_50, RDN60, RDN136	
602	602	G	R		Schm2_46	
605	605	R	K		Schm1_174	
610	610	A	V		Schm1_74, Schm1_76, Schm1_35, Schm1_176, Schm1_25, Schm1_41, Schm2_9, Schm2_32, RDN136, RDN78	
636	636	L	M		Schm1_74, Schm1_76, Schm1_35, Schm1_176, Schm1_25, Schm1_41, Schm2_9, Schm2_32, RDN136, RDN78	
640	640	E	K		Schm1_74, Schm1_76, Schm1_35, Schm1_176, Schm1_25, Schm1_41, Schm2_9, Schm2_32, RDN136, RDN78	
641	641	A	V		Schm1_56,	

					Schm1_108	
650	650	V	E		Schm2_9	
666	666	F	L		Schm1_22	
700	700	A	T		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_253, Schm1_68, Schm1_108, Schm1_156, Schm1_248, Schm1_3, Schm1_22, Schm1_29, Schm1_59, Schm1_97, Schm1_123, Schm1_136, Schm2_23, Schm2_30, RDN02, RDN120, RDN116	
703	703	A	V		Schm2_50, RDN60	
710	710	S	G		Schm1_17, Schm1_59, Schm1_97	
733	733	E	G		Schm1_56, Schm1_108	
750	750	A	P		Schm1_22	
752	752	P	S		Schm1_55, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_35, Schm1_68, Schm1_176, Schm1_177, Schm1_234, Schm1_3, Schm1_25, Schm1_41, Schm1_43, Schm1_99, Schm1_103, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, RDN136, RDN78	
758	758	P	L		Schm1_92	
764	764	I	V		Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194,	

					Schm1_35, Schm1_176, Schm1_177, Schm1_234, Schm1_25, Schm1_41, Schm1_43, Schm1_99, Schm1_103, Schm2_9, Schm2_14, Schm2_32, Schm2_46, RDN136, RDN78	
765	765	D	E		Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_35, Schm1_176, Schm1_177, Schm1_234, Schm1_25, Schm1_41, Schm1_43, Schm1_99, Schm1_103, Schm2_9, Schm2_14, Schm2_32, Schm2_46, RDN136, RDN78	
794	794	L	F	H	Schm1_22	Schm2_23, Schm2_30
873	873	K	R		Schm1_55, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_35, Schm1_68, Schm1_141, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_3, Schm1_25, Schm1_41, Schm1_43, Schm1_99, Schm1_103, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50,	

					RDN60, RDN136, RDN78, RDN75	

Sequence analyses of Spy0292

Sequences were obtained from all 51 strains. The level of amino acid sequence identity ranged from 97.3% to 100% as compared to the sequence of Spy0292 from *S. pyogenes* SF370. Table 6 lists all 36 amino acid positions which showed a distinct amino acid as compared to Spy0292 from *S. pyogenes* SF370.

Table 6: Gene conservation of Spy0292. [1], observed amino acid at respective position in any of the sequenced genes of the respective *S. pyogenes* strains. [2], second possible amino acid observed at the respective position. [3], third possible amino acid observed at the respective position.

Position in SF370 gene	Alignment position	Amino acid in SF370 gene	AA change[1]	AA change[2]	AA change[3]	Strains with respective change[1]	Strains with respective change[2]	Strains with respective change[3]
21	21	S	N			Schm1_136		
32	32	A	V			RDN02		
45	45	E	K			RDN60		
48	48	A	T			Schm1_56, Schm1_108, Schm1_85		
50	50	E	K			RDN75		
57	57	V	I			Schm2_50		
58	58	S	T			Schm2_50		
65	65	L	M			Schm1_141, Schm1_156, Schm1_174		
68	68	K	Q	N		Schm2_30	Schm2_50	
88	88	Y	D			Schm2_30		
89	89	E	D			Schm2_30		
93	93	N	Y			Schm2_50		
95	95	T	S			Schm2_30		
96	96	I	M			Schm2_30		
101	101	L	P			Schm2_30		
121	121	N	I			Schm2_50		
122	122	S	T			Schm2_50		
128	128	A	P	S		RDN60	RDN60	
137	137	K	N			Schm2_30		
141	141	K	E	Q		Schm1_17	Schm2_50	
147	147	R	L	W	I	Schm1_17	Schm2_50	RDN60
148	148	Q	L			Schm2_30, RDN60		
152	152	S	F			RDN120		
154	154	A	T			Schm1_55, Schm1_68, Schm1_3, Schm1_29, Schm2_23, Schm2_30		
165	165	H	L			RDN60		

188	188	L	F			Schm1_174		
189	189	A	P			Schm1_174		
190	190	I	V			Schm1_253, Schm1_123		
214	214	A	D			Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_25, Schm1_43, Schm1_59, Schm1_85, Schm1_99, Schm1_103, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN120		
240	240	V	I			Schm1_92, RDN120		
266	266	L	I			Schm1_144, Schm1_234, Schm1_103		
309	309	Y	S			Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97,		

						Schm1_99, Schm1_103, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116		
314	314	P	S			Schm1_17, Schm1_22, Schm1_97		
351	351	A	P			Schm1_177		
371	371	G	A			Schm1_234		
386	386	Q	H			Schm1_234		

Sequence analyses of Spy0416

Sequences were obtained from all 50 strains excluding strain Schmitz 1/74. The level of amino acid sequence identity ranged from 98.1% to 100% as compared to the sequence of Spy0416 from *S. pyogenes* SF370. Table 7 lists all 103 amino acid positions which showed a distinct amino acid as compared to Spy0416 from *S. pyogenes* SF370. The gene showed in addition an insertion of 2 amino acids after position 31, as well as several deletions of amino acids at the indicated positions (e.g. strains Schmitz 1/17 and Schmitz 1/39).

Table 7: Gene conservation of Spy0416. [1], observed amino acid at respective position in any of the sequenced genes of the respective *S. pyogenes* strains. [2], second possible amino acid observed at the respective position. Deletion or insertion refers to a missing or additional amino acid relative to Spy0416 of *S. pyogenes* SF370.

Position in SF370 gene	Alignment position	Amino acid in SF370 gene	AA change[1]	AA change[2]	Strains with respective change[1]	Strains with respective change[2]
21	21	I	V		Schm1_99, Schm2_46	
27	27	V	M		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_142, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156,	

					Schm1_174, Schm1_176, Schm1_177, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN136, RDN78, RDN120, RDN75, RDN116	
29	29	T	M		Schm1_17, Schm1_39, Schm1_76, Schm1_142, Schm1_35, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_248, Schm1_22, Schm1_25, Schm1_41, Schm1_43, Schm1_59, Schm1_97, Schm1_136, Schm2_9, Schm2_14, RDN136, RDN78, RDN75	
Insertion	32	-	T		Schm1_17, Schm1_39, Schm1_76, Schm1_142, Schm1_35, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_248, Schm1_22, Schm1_25, Schm1_41,	

					Schm1_43, Schm1_59, Schm1_97, Schm1_136, Schm2_9, Schm2_14, RDN136, RDN78	
Insertion	33	-	T		Schm1_17, Schm1_22, Schm1_97	
38	40	S	T		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_142, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN136, RDN78, RDN116	
40	42	M	T		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_142, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177,	

					Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN136, RDN78, RDN116	
49	51	A	T		Schm1_39, Schm1_76, Schm1_142, Schm1_35, Schm1_176, Schm1_177, Schm1_248, Schm1_25, Schm1_41, Schm1_43, Schm1_59, Schm2_9, Schm2_14, Schm2_32, RDN60, RDN136, RDN78	
54	56	Q	P		Schm1_55, Schm1_68, Schm1_3, Schm1_29, Schm2_23, Schm2_30	
55	57	H	P		Schm1_55, Schm1_253, Schm1_68, Schm1_3, Schm1_29, Schm1_99, Schm1_123, Schm2_23, Schm2_30, Schm2_32, Schm2_46, RDN116	
67	69	K	Q		Schm1_17, Schm1_55, Schm1_56, Schm1_253, Schm1_68, Schm1_108,	

					Schm1_3, Schm1_22, Schm1_29, Schm1_85, Schm1_97, Schm1_99, Schm1_123, Schm1_136, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN120, RDN116	
68	70	S	P	T	Schm1_39, Schm1_55, Schm1_76, Schm1_142, Schm1_35, Schm1_68, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_248, Schm1_3, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm2_9, Schm2_14, Schm2_23, Schm2_30, RDN136, RDN78, RDN75	Schm1_92
69	71	Q	P		Schm1_17, Schm1_56, Schm1_253, Schm1_108, Schm1_22, Schm1_85, Schm1_97, Schm1_99, Schm1_123, Schm1_136, Schm2_32, Schm2_46, Schm2_50, RDN120, RDN116	
71	73	T	I		Schm1_253, Schm1_123, Schm2_32	
74	76	I	V		Schm1_55, Schm1_253, Schm1_68, Schm1_3, Schm1_29, Schm1_99, Schm1_123, Schm1_136,	

					Schm2_23, Schm2_30, Schm2_46	
76	78	L	P		Schm1_17, Schm1_55, Schm1_56, Schm1_92, Schm1_144, Schm1_194, Schm1_253, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_234, Schm1_3, Schm1_22, Schm1_29, Schm1_85, Schm1_97, Schm1_99, Schm1_123, Schm1_136, Schm2_23, Schm2_30, Schm2_46, Schm2_50, RDN60, RDN02, RDN116	
77	79	K	E		Schm1_55, Schm1_253, Schm1_68, Schm1_3, Schm1_29, Schm1_99, Schm1_123, Schm1_136, Schm2_23, Schm2_30, Schm2_46	
78	80	T	I		Schm1_56, Schm1_108, Schm1_85, Schm2_50	
85	87	S	P		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_176, Schm1_177, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41,	

					Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_50, RDN60, RDN136, RDN78	
87	89	D	G		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_176, Schm1_177, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_50, RDN60, RDN136, RDN78	
91	93	E	K		Schm1_99, Schm2_46, RDN116	
93	95	T	Deletion		RDN60	
102	104	A	S		RDN120, RDN75, RDN116	
104	106	S	P		Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_142, Schm1_253, Schm1_35, Schm1_68, Schm1_108,	

					Schm1_176, Schm1_177, Schm1_248, Schm1_3, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_99, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN136, RDN78, RDN120, RDN75, RDN116	
107	109	N	Deletion		Schm1_92	
110	112	S	P		Schm1_17, Schm1_39, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_253, Schm1_35, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_248, Schm1_22, Schm1_25, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN136, RDN78, RDN120, RDN75, RDN116	
183	185	A	V		RDN75	

215	217	E	G		Schm1_17, Schm1_92, Schm1_22, Schm1_97, Schm1_99, Schm2_46, RDN116	
228	230	A	Deletion		Schm1_17, Schm1_56, Schm1_92, Schm1_108, Schm1_22, Schm1_85, Schm1_97, Schm2_50, RDN120	
229	231	E	Deletion	D	Schm1_17, Schm1_56, Schm1_92, Schm1_108, Schm1_22, Schm1_85, Schm1_97, Schm2_50, RDN120, RDN116	Schm1_144, Schm1_194, Schm1_253, Schm1_234, Schm1_99, Schm1_123, Schm1_136, Schm2_46, RDN02
230	232	A	Deletion		RDN116	
238	240	H	N		Schm1_17, Schm1_92, Schm1_22, Schm1_97	
273	275	D	E		Schm1_92, Schm1_99, Schm2_46, RDN120, RDN116	
308	310	A	T		Schm1_56, Schm1_108, Schm1_85, Schm2_50	
320	322	I	V		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41,	

					Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
428	430	T	A		Schm1_142	
429	431	V	A		Schm1_17, Schm1_22, Schm1_97	
431	433	E	G		Schm1_253, Schm1_123	
434	436	N	S		RDN116	
449	451	V	F		Schm1_177	
453	455	D	N		Schm1_142, Schm1_35, Schm1_141, Schm1_174, Schm1_176, Schm1_177, Schm1_248, Schm1_25, Schm1_41, Schm1_43, Schm1_59, Schm1_97, Schm1_123, Schm1_136, Schm2_9, RDN136	
463	465	S	T		Schm1_177, RDN136	
478	480	N	K		Schm1_17, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_176, Schm1_177, Schm1_234, Schm1_22, Schm1_25, Schm1_43, Schm1_97, RDN60, RDN02, RDN136, RDN120, RDN116	

481	483	D	N		Schm1_55, Schm1_68, Schm1_3, Schm1_29, Schm1_136, Schm2_23, Schm2_30	
484	486	G	D		Schm1_17, Schm1_92, Schm1_144, Schm1_194, Schm1_234, Schm1_22, Schm1_97, RDN02	
493	495	P	L		RDN120	
512	514	V	L		Schm1_253, Schm1_123	
519	521	P	S		Schm1_253, Schm1_123	
530	532	A	S		Schm1_141, Schm1_156, Schm1_174	
535	537	I	V		RDN120	
547	549	A	V		Schm1_35, Schm1_41, Schm2_9	
553	555	G	T		RDN116	
560	562	E	V		RDN02, RDN116	
630	632	V	I		RDN75	
668	670	T	M		RDN116	
689	691	G	D		Schm1_39, Schm1_248, Schm1_59, Schm2_14	
706	708	I	V		RDN02	
723	725	D	A		Schm1_39, Schm1_55, Schm1_56, Schm1_92, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_234, Schm1_248, Schm1_3, Schm1_29, Schm1_41, Schm1_59, Schm1_85, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_50, RDN60,	

					RDN02, RDN78, RDN120, RDN116	
734	736	T	A		RDN02	
743	745	R	H		RDN116	
749	751	H	R		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
770	772	R	K		RDN60, RDN120	
804	806	D	A		Schm1_55, Schm1_68, Schm1_248, Schm1_3, Schm1_29, Schm2_23, Schm2_30, RDN02, RDN120, RDN75	
874	876	T	M		Schm1_35,	

					Schm1_41, Schm1_103, Schm1_136, Schm2_9, RDN78	
876	878	S	C		Schm1_94	
913	915	N	S		RDN60	
951	953	P	S		Schm1_76, Schm1_177, Schm1_43	
991	993	H	Y		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_142, Schm1_144, Schm1_194, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_46, Schm2_50, RDN60, RDN02, RDN78, RDN120, RDN116	
1053	1055	V	A		Schm1_94, Schm1_12X, Schm1_5	
1078	1080	E	A		Schm1_92, Schm1_142, Schm1_176, Schm1_25, Schm1_99, Schm2_23, Schm2_30, Schm2_46	
1080	1082	N	S		Schm1_35, Schm1_41, Schm2_9, RDN78	
1227	1229	T	I		Schm1_76	
1238	1240	V	A		Schm1_17, Schm1_39,	

					Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
1241	1243	I	V		Schm1_253, Schm1_123	
1302	1304	D	G		Schm1_253, Schm1_123	
1313	1315	D	G		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_94, Schm1_142, Schm1_144, Schm1_253, Schm1_12X, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156,	

					Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_5, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
1322	1324	V	I		RDN120	
1349	1351	V	M		RDN02	
1355	1357	P	S		Schm1_234, Schm1_136, RDN75	
1364	1366	R	E		Schm1_156	
1365	1367	D	I		Schm1_156	
1393	1395	A	V		Schm1_35, Schm1_41, Schm2_9, RDN78	
1425	1427	A	V		RDN02	
1479	1481	N	K		RDN60	
1483	1485	V	I		Schm1_141, Schm1_156, Schm1_174	
1487	1489	I	M		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174,	

					Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
1505	1507	E	K		Schm2_50	
1516	1518	D	G		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136,	

					Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
1522	1524	E	G		Schm1_99, Schm2_32, Schm2_46	
1538	1540	G	D		Schm1_17, Schm1_22, Schm1_97	
1545	1547	S	T		Schm2_50	
1555	1557	N	D		Schm1_35, Schm1_41, Schm2_9, RDN78	
1560	1562	T	A		Schm1_17, Schm1_144, Schm1_194, Schm1_35, Schm1_234, Schm1_22, Schm1_41, Schm1_97, Schm1_99, Schm1_103, Schm1_136, Schm2_9, Schm2_32, Schm2_46, RDN78	
1576	1578	G	R		Schm2_50	
1580	1582	D	G		Schm1_144, Schm1_194, Schm1_234, Schm1_136	
1587	1589	V	A		Schm1_142, Schm1_176, Schm1_25	
1591	1593	N	S		RDN75	
1598	1600	A	V		Schm1_17, Schm1_22, Schm1_97	
1605	1607	S	T		Schm1_17, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108,	

					Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
1608	1610	S	P		Schm1_144, Schm1_194, Schm1_234, Schm1_136	
1609	1611	A	Deletion		Schm1_142, Schm1_176, Schm1_25, RDN120	
1610	1612	T	Deletion		Schm1_142, Schm1_176, Schm1_25, RDN120	
1617	1619	T	A		Schm1_17, Schm1_39, Schm1_56, Schm1_92, Schm1_35, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_248, Schm1_22, Schm1_41, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm2_9, Schm2_14, Schm2_23,	

					Schm2_30, Schm2_46, Schm2_50, RDN60, RDN78, RDN116	
1622	1624	G	S		Schm1_142, Schm1_176, Schm1_25, RDN120	
1642	1644	K	T		Schm1_144	

Sequence analyses of Spy0488

Sequences were obtained from all 51 strains. The level of amino acid sequence identity ranged from 85.4% to 100% as compared to the sequence of Spy0488 from *S. pyogenes* SF370. Table 8 lists all 49 amino acid positions which showed a distinct amino acid as compared to Spy0488 from *S. pyogenes* SF370. The genes from several strains (e.g. Schmitz 1/55) possessed furthermore a different N terminus, with an addition of 25 amino acids and a frame-shift for the first 16 amino acids relative to Spy0488 from *S. pyogenes* SF370.

Table 8: Gene conservation of Spy0488. [1], observed amino acid at respective position in any of the sequenced genes of the respective *S. pyogenes* strains. [2], second possible amino acid observed at the respective position. Insertion refers to an additional amino acid relative to Spy0488 of *S. pyogenes* SF370.

Position in SF370 gene	Alignment position	Amino acid in SF370 gene	AA change[1]	AA change[2]	Strains with respective change[1]	Strains with respective change[2]
Insertion	1	-	M		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85,	

					Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	2	-	M		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	3	-	M		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177,	

					Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	4	-	L		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	5	-	R		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	6	-	D		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174,	

					Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	7	-	V		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	8	-	K		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	9	-	V		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141,	

					Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	10	-	K		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	11	-	M	T	Schm1_39, Schm1_55, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, RDN60, RDN136, RDN78, RDN120, RDN75	Schm1_56, Schm1_108, Schm1_22, Schm1_85, Schm1_97, Schm2_50, RDN02, RDN116
Insertion	12	-	S		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177,	

					Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	13	-	S		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	14	-	L		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	15	-	L		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174,	

					Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	16	-	V		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	17	-	G		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	18	-	C		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141,	

					Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	19	-	A		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	20	-	A		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	21	-	T		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68,	

					Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	22	-	L		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	23	-	L		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	24	-	V		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253,	

					Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
Insertion	25	-	S		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
2	27	R	S		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
3	28	Q	S	G	Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_142, Schm1_253, Schm1_68, Schm1_108,	Schm1_74, Schm1_92, Schm1_144, Schm1_194,

					Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_123, Schm1_136, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN120, RDN75, RDN116	Schm1_35, Schm1_234, Schm1_41, Schm1_103, Schm2_9, RDN78
4	29	I	T		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
5	30	Q	V		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
6	31	S	A		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174,	

					Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
7	32	I	A		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
8	33	R	D		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
9	34	L	S		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141,	

					Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
10	35	I	V		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
11	36	D	H		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
12	37	V	S		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68,	

					Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
13	38	L	S		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN120, RDN75, RDN116	RDN78
14	39	E	D		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
15	40	L	R		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253,	

					Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
16	41	A	R		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
30	55	S	F		Schm1_99, Schm1_136, Schm2_46	
35	60	S	Y		RDN75	
50	75	A	T		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
53	78	N	D		Schm1_253, Schm1_99, Schm1_123, Schm1_136,	

					Schm2_46, RDN120	
56	81	S	Y		Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_144, Schm1_194, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_29, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_136, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN120, RDN75, RDN116	
60	85	D	G		Schm1_248, Schm1_59	
69	94	D	G		Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_92, Schm1_253, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_177, Schm1_248, Schm1_3, Schm1_22, Schm1_29, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_123, Schm1_136, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN120	
75	100	Q	H		Schm2_32	
76	101	I	T		Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_144, Schm1_194, Schm1_253, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_29, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN120	
87	112	F	L		Schm1_253, Schm1_123	
93	118	G	E		Schm1_99, Schm2_46	
112	137	V	A		Schm1_253, Schm1_123	
117	142	I	T		Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_177, Schm1_248, Schm1_3, Schm1_22, Schm1_29,	

					Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_123, Schm1_136, Schm2_9, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116	
127	152	H	Y		Schm1_39	
157	182	D	G		RDN75	
163	188	V	L		RDN75	
174	199	K	T		Schm1_55, Schm1_68, Schm1_3, Schm1_29, Schm2_23, Schm2_30	
183	208	G	R		RDN75	
184	209	G	S		Schm1_56, Schm1_108, Schm1_85, Schm2_50, RDN02	
188	213	F	L		Schm1_92, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_234, Schm1_41, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_46, RDN78	
198	223	P	S		Schm1_92	
199	224	K	R		Schm1_56, Schm1_108, Schm1_85, Schm2_50, RDN02	
201	226	R	G		Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_108, Schm1_177, Schm1_234, Schm1_41, Schm1_43, Schm1_85, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_32, Schm2_46, Schm2_50, RDN02, RDN136, RDN78, RDN120	
202	227	Q	L		Schm1_144, Schm1_194, Schm1_35, Schm1_234, Schm1_41, Schm1_99, Schm1_103, Schm1_136, Schm2_9, Schm2_46, RDN78	
206	231	T	I		Schm1_56, Schm1_108, Schm1_85, Schm2_50, RDN02	
209	234	D	A		Schm1_92, Schm1_144, Schm1_194, Schm1_35, Schm1_234, Schm1_41, Schm1_99, Schm1_103, Schm1_136, Schm2_9, Schm2_46, RDN78	
217	242	P	S		Schm1_56, Schm1_108, Schm1_85, Schm2_50, RDN02	
221	246	W	C		Schm1_76, Schm1_177, Schm1_43, RDN136	
222	247	K	E		Schm1_56, Schm1_108,	

					Schm1_85, Schm2_50, RDN02	
232	257	A	T		Schm1_39, Schm1_22, Schm1_97	
235	260	S	F		Schm1_253, Schm1_123	
238	263	T	I		Schm1_248, Schm1_59	
258	283	A	V		Schm1_92	
291	316	E	Q		Schm1_55, Schm1_68, Schm1_3, Schm1_29, Schm2_23, Schm2_30	

Sequence analyses of Spy0872

Sequences were obtained from all 51 strains. The level of amino acid sequence identity ranged from 98.2% to 100% as compared to the sequence of Spy0872 from *S. pyogenes* SF370. Table 9 lists all 34 acid positions which showed a distinct amino acid as compared to Spy0872 from *S. pyogenes* SF370. The gene from strain Schmitz 1/22 showed in addition an insertion of 2 amino acids after position 587.

Table 9: Gene conservation of Spy0872. [1], observed amino acid at respective position in any of the sequenced genes of the respective *S. pyogenes* strains. Insertion refers to an additional amino acid relative to Spy0872 of *S. pyogenes* SF370.

Position in SF370 gene	Alignment position	Amino acid in SF370 gene	AA change[1]	Strains with respective change[1]
67	67	G	C	Schm1_136
74	74	E	D	Schm1_76, Schm1_177, Schm1_43, RDN136
178	178	K	N	Schm1_7, Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
181	181	P	S	RDN60
222	222	H	Y	RDN120
228	228	V	A	Schm1_56, Schm1_108, Schm1_85, Schm2_50
253	253	V	I	Schm1_7, Schm1_39, Schm1_55, Schm1_56, Schm1_76, Schm1_142, Schm1_144, Schm1_194, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm2_14, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN136, RDN120
328	328	I	M	Schm1_55, Schm1_56, Schm1_92, Schm1_68, Schm1_108, Schm1_3, Schm1_29, Schm1_85, Schm1_136, Schm2_23, Schm2_30, Schm2_50, RDN75

329	329	K	T	Schm1_55, Schm1_56, Schm1_92, Schm1_68, Schm1_108, Schm1_3, Schm1_29, Schm1_85, Schm1_136, Schm2_23, Schm2_30, Schm2_50, RDN75
336	336	V	I	Schm1_56, Schm1_108, Schm1_85, Schm2_50
337	337	A	T	Schm1_136, RDN75
340	340	P	L	RDN120
393	393	A	V	Schm1_7, Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
412	412	M	I	RDN120
427	427	D	Y	Schm2_46
433	433	G	E	Schm1_7, Schm1_22, Schm1_97
444	444	I	T	RDN75
478	478	Y	F	Schm1_253, Schm1_123
490	490	T	I	Schm1_55, Schm1_68, Schm1_3, Schm1_29, Schm2_23, Schm2_30
492	492	F	C	RDN02
532	532	A	T	Schm1_144, Schm1_194, Schm1_234, Schm1_103
535	535	I	V	Schm1_142, Schm1_176, Schm1_25, Schm2_46, RDN116
553	553	E	Q	Schm1_142, Schm1_176, Schm1_25, Schm1_99, Schm2_32, Schm2_46, RDN116
576	576	S	R	Schm1_142, Schm1_176, Schm1_25, Schm1_99, Schm2_46, RDN116
580	580	V	I	Schm1_142, Schm1_176, Schm1_25, Schm1_99, Schm2_46, RDN116
Insertion	588	-	I	Schm1_7, Schm1_22, Schm1_97
Insertion	589	-	I	Schm1_7, Schm1_22, Schm1_97
588	590	I	T	RDN78
598	600	G	D	Schm1_92
600	602	T	I	Schm1_7, Schm1_39, Schm1_55, Schm1_56, Schm1_74, Schm1_76, Schm1_92, Schm1_142, Schm1_144, Schm1_194, Schm1_253, Schm1_35, Schm1_68, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_176, Schm1_177, Schm1_234, Schm1_248, Schm1_3, Schm1_22, Schm1_25, Schm1_29, Schm1_41, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_99, Schm1_103, Schm1_123, Schm1_136, Schm2_9, Schm2_14, Schm2_23, Schm2_30, Schm2_32, Schm2_46, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120, RDN75, RDN116
605	607	V	I	Schm1_7, Schm1_39, Schm1_56, Schm1_76, Schm1_144, Schm1_194, Schm1_253, Schm1_108, Schm1_141, Schm1_156, Schm1_174, Schm1_177, Schm1_234, Schm1_248, Schm1_22, Schm1_43, Schm1_59, Schm1_85, Schm1_97, Schm1_103, Schm1_123, Schm2_14, Schm2_50, RDN60, RDN02, RDN136, RDN78, RDN120
620	622	L	F	Schm1_7, Schm1_142, Schm1_176, Schm1_22, Schm1_25, Schm1_97, Schm1_99, Schm2_32, Schm2_46, RDN116
625	627	T	I	Schm1_7, Schm1_22, Schm1_97
634	636	S	N	Schm1_7, Schm1_142, Schm1_176, Schm1_22, Schm1_25, Schm1_97, Schm1_99, Schm2_46, RDN116

659	661	G	C	Schm1_253, Schm1_123
667	669	K	E	Schm1_144, Schm1_194, Schm1_234, Schm1_103, RDN120

Sequence analyses of Spy0895

Sequences were obtained from all 51 strains. The level of amino acid sequence identity ranged from 98.9% to 100% as compared to the sequence of Spy0895 from *S. pyogenes* SF370. Table 10 lists all 13 amino acid positions which showed a distinct amino acid as compared to Spy0895 from *S. pyogenes* SF370.

Table 10: Gene conservation of Spy0895. [1], observed amino acid at respective position in any of the sequenced genes of the respective *S. pyogenes* strains.

Position in SF370 gene	Alignment position	Amino acid in SF370 gene	AA change[1]	Strains with respective change[1]
19	19	A	V	Schm1_17, Schm1_22, Schm1_97
33	33	A	V	Schm1_17, Schm1_141, Schm1_156, Schm1_174, Schm1_22, Schm1_97, RDN02
50	50	F	V	Schm1_253, Schm1_123
52	52	A	V	Schm1_17, Schm1_55, Schm1_68, Schm1_141, Schm1_156, Schm1_174, Schm1_3, Schm1_22, Schm1_29, Schm1_97, Schm2_30
60	60	T	I	Schm1_56, Schm1_108, Schm1_85, Schm2_50
71	71	L	I	Schm1_92, Schm1_144, Schm1_194, Schm1_234, Schm1_103
138	138	H	Q	Schm1_92, Schm1_144, Schm1_194, Schm1_234, Schm1_103
188	188	R	P	Schm1_174
238	238	R	C	Schm1_55, Schm1_76, Schm1_68, Schm1_177, Schm1_3, Schm1_29, Schm1_43, Schm2_30, RDN136
242	242	Y	C	Schm1_136
252	252	K	T	Schm1_56, Schm1_108, Schm1_85, Schm2_50
255	255	S	G	Schm1_56, Schm1_108, Schm1_85, Schm2_50
256	256	L	F	RDN60

Sequence analyses of Spy1536

Sequences were obtained from all 51 strains. The level of amino acid sequence identity ranged from 99.1% to 100% as compared to the sequence of Spy1536 from *S. pyogenes* SF370. Table 11 lists all 8 amino acid positions which showed a distinct amino acid as compared to Spy1536 from *S. pyogenes* SF370. The gene from strain Schmitz 2/14 showed in addition an insertion of 3 amino acids after position 207.

Table 11: Gene conservation of Spy1536. [1], observed amino acid at respective position in any of the sequenced genes of the respective *S. pyogenes* strains. Insertion refers to an additional amino acid relative to Spy1536 of *S. pyogenes* SF370.

Position in SF370 gene	Alignment position	Amino acid in SF370 gene	AA change[1]	Strains with respective change[1]
5	5	K	N	Schm1_12, Schm2_9, Schm1_136
92	92	G	R	Schm1_142
97	97	A	T	Schm1_5, Schm1_74
125	125	P	S	Schm1_123
126	126	V	A	Schm1_142
183	183	V	I	Schm1_94, RDN78, Schm1_97, Schm1_59, Schm1_76, RDN136, Schm1_177, Schm2_32, Schm1_141, Schm1_144, RDN120, Schm1_25, Schm1_176, RDN75_85, Schm2_46, Schm2_23, Schm1_55
Insertion	208	-	K	Schm2_14
Insertion	209	-	N	Schm2_14
Insertion	210	-	G	Schm2_14
333	336	V	I	Schm1_12, Schm1_35, Schm2_9, Schm1_174, Schm1_136, Schm1_234, Schm1_68
337	340	Q	E	Schm1_43, Schm1_108

Sequence analyses of Spy1666

Sequences were obtained from 50 strains. The sequence from strain RDN120 was not determined. The level of amino acid sequence identity ranged from 98.2 to 100% as compared to the sequence of Spy1666 from *S. pyogenes* SF370. Table 12 lists all 18 amino acid positions which showed a distinct amino acid as compared to Spy1666 from *S. pyogenes* SF370.

Table 12: Gene conservation of Spy1666. [1], observed amino acid at respective position in any of the sequenced genes of the respective *S. pyogenes* strains.

Position in SF370 gene	Alignment position	Amino acid in SF370 gene	AA change[1]	Strains with respective change[1]
3	3	S	P	Schm1_17, Schm1_22, Schm1_97, Schm1_136, Schm1_17, Schm1_22, Schm1_97, Schm1_136
11	11	L	V	Schm1_17, Schm1_22, Schm1_97, Schm1_136, Schm1_17, Schm1_22, Schm1_97, Schm1_136
45	45	D	N	Schm1_17, Schm1_22, Schm1_97, Schm1_136, Schm1_17, Schm1_22, Schm1_97, Schm1_136
67	67	G	S	Schm1_17, Schm1_22, Schm1_97, Schm1_136, Schm1_17, Schm1_22, Schm1_97, Schm1_136
69	69	E	Q	Schm1_17, Schm1_22, Schm1_97, Schm1_136, Schm1_17, Schm1_22, Schm1_97, Schm1_136
90	90	K	Q	Schm1_142, Schm1_176, Schm1_25, Schm2_46, Schm1_142, Schm1_176, Schm1_25, Schm2_46
106	106	R	I	RDN136, RDN78, RDN136, RDN78

120	120	I	F	Schm1_136, Schm1_136
149	149	L	S	RDN78, RDN78
167	167	T	N	RDN75, RDN75
204	204	T	A	Schm1_253, Schm1_103, Schm1_123, Schm1_253, Schm1_103, Schm1_123
217	217	P	S	Schm1_39, Schm1_248, Schm1_59, Schm1_39, Schm1_248, Schm1_59
251	251	Q	H	Schm1_97, Schm1_97
252	252	D	E	Schm1_76, Schm1_141, Schm1_156, Schm1_174, Schm1_177, Schm1_43, Schm2_32, RDN136, Schm1_76, Schm1_141, Schm1_156, Schm1_174, Schm1_177, Schm1_43, Schm2_32, RDN136
259	259	L	F	Schm1_92, RDN75, Schm1_92, RDN75
292	292	L	F	RDN116, RDN116
302	302	K	T	Schm1_17, Schm1_142, Schm1_176, Schm1_22, Schm1_25, Schm1_97, Schm2_46, Schm1_17, Schm1_142, Schm1_176, Schm1_22, Schm1_25, Schm1_97, Schm2_46
319	319	T	A	Schm1_76, Schm1_141, Schm1_156, Schm1_174, Schm1_177, Schm1_43, Schm2_32, RDN136, Schm1_76, Schm1_141, Schm1_156, Schm1_174, Schm1_177, Schm1_43, Schm2_32, RDN136

Sequence analyses of Spy1727

No sequence variation was observed on the amino acid sequence level in any of the analyzed 51 gene sequences obtained from the listed *S. pyogenes* strains.

SEQUENCE DATA FOR AMINO ACID SEQUENCES

1. Spy0269

1.1 Full length Spy0269

> Spy0269 / SF370 (serotype 1); SEQ ID NO: 57
MDLEQTKPNQVKQKIALTSTIALLSASVGVSHQVKADDRASGETKASNTHDDSLPKPETIQEAKATIDAVEKT
LSQQKAELTELATALTKTTAEINHLKEQQDNEQKALTSAQEIYTNTLASSEETLLAQGAEHQRELTATETELH
NAQADQHSKETALSEQKASISAETTRAQDLVEQVKTSEQNIAKLNAMISNPDAITKAAQTANDNTKALSSELE
KAKADLENQKAKVKKQLTEELAAQKAALAEKEAELSRLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASG
YIGSASYNNYYKEHADQIIAKASPGNQLNQYQDIPADRNRFVDPDNLTPEVQNELAQFAAHMINSVRRQLGLP
PVTVTAGSQEFARLLSTSYKKTHGNTRPSFVYGQPGVSGHYGVGPHDKTIIEDSAGASGLIRNDDNMYENIGA
FNDVHTVNGIKRGIYDSIKYMLFTDHLHGNTYGHAINFLRVDKHNPNAPVYLGFSTSNVGSLNEHFVMFPESN
IANHQRFNKTPIKAVGSTKDYAQRVGTVSDTIAAIKGKVSSLENRLSAIHQEADIMAAQAKVSQLQGKLASTL
KQSDSLNLQVRQLNDTKGSLRTELLAAKAKQAQLEATRDQSLAKLASLKAALHQTEALAEQAAARVTALVAKK
AHLQYLRDFKLNPNRLQVIRERIDNTKQDLAKTTSSLLNAQEALAALQAKQSSLEATIATTEHQLTLLKTLAN
EKEYRHLDEDIATVPDLQVAPPLTGVKPLSYSKIDTTPLVQEMVKETKQLLEASARLAAENTSLVAEALVGQT
SEMVASNAIVSKITSSITQPSSKTSYGSGSSTTSNLISDVDESTQRALKAGVVMLAAVGLTGFRFRKESK

1.2 Antigenic fragment Spy0269-1

> Spy0269-1 / SF370 (serotype 1); SEQ ID NO: 1
DDRASGETKASNTHDDSLPKPETIQEAKATIDAVEKTLSQQKAELTELATALTKTTAEINHLKEQQDNEQKAL
TSAQEIYTNTLASSEETLLAQGAEHQRELTATETELHNAQADQHSKETALSEQKASISAETTRAQDLVEQVKT
SEQNIAKLNAMISNPDAITKAAQTANDNTKALSSELEKAKADLENQKAKVKKQLTEELAAQKAALAEKEAELS
RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNNYYKEHADQIIAKASPGNQLNQYQDIPA
DRNRFVDPDNLTPEVQNELAQFAAHMINSVRRQLGLPPVTVTAGSQEFARLLSTSYKKTHGNTRPSFVYGQPG
VSGHYGVGPHDKTIIEDSAGASGLIRNDDNMYENIGAFNDVHTVNGIKRGIYDSIKYMLFTDHLHGNTYGHAI
NFLRVDKHNPNAPV

1.3 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0269-1 / Schmitz 2/14 (serotype 1); SEQ ID NO: 58
DDRASGETKASNTHDDSLPKPETIQEAKATIDAVEKTLSQQKAELTELATALTKTTAEINNLKEQQDNEQKAL
TSAQEIYTNTLASSEETLLAQGAEHQRELTATETELHNAQADQHSKETALSEQKASISAETTRAQDLVEQVKT
SEQNIAKLNAMISNPDAITKAAQTANDNTKALSSELEKAKADLENQKAKVKKQLTEELAAQKAALAEKEAELS
RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNNYYKEHADQIIAKASPGNQLNQYQDIPA
DRNRFVDPDNLTPEVQNELAQFAAHMINSVRRQLGLPPVTVTAGSQEFARLLSTSYKKTHGNTRPSFVYGQPG
VSGHYGVGPHDKTIIEDSAGASGLIRNDDNMYENIGAFNDVHTVNGIKRGIYDSIKYMLFTDHLHGNTYGHAI
NFLRVDKRNPNAPV

> Spy0269-1 / Schmitz 1/156 (serotype 4); SEQ ID NO: 59
DDRASGETKASNTHDDSLPKPETIQEAKATIDAVEKTLSQQKAELTELATALTKTTAEINHLKEQQDNEQKAL
TSAQEIYTNTLASSEETLLAQGAEHQRELTATETELHNAQADQHSKETALSEQKASISAETTRAQDLVEQVKT
SEQNIAKLNAMISNPDAITKAAQTANDNTKALSSELEKAKADLENQKAKVKKQLTEELAAQKAALAEKEAELS
RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNNYYKEHADQIIAKASPGNQLNQYQDIPA
DRNRFVDPDNLTPEVQNELAQFAAHMINSVRRQLGLPPVTVTAGSQEFARLLSTSYKKTHGNTRPSFVYGQPG
VSGHYGVGPHDKTIIEDSAGASGLIRNDDNMYENIGAFNDVHTVNGIKRGIYDSIKYMLFTDHLHGNTYGHAI
NFLRVDKHNPKAPV

> Spy0269-1 / Schmitz 1/59 (serotype 12); SEQ ID NO: 60
DDRASGETKASNTHDDSLPKPETIQEAKATIDAVEKTLSQQKAELTKLATALTKTTAEINHLKEQQDNEQKAL
TSAQEIYTNTLASSEETLLAQGAEHQRELTATETELHNAQADQHSKETALSEQKASISAETTRAQDLVEQVKT
SEQNIAKLNAMISNPDAITKAAQTANDNTKALSSELEKAKADLENQKAKVKKQLTEELAAQKAALAEKEAELS
RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNNYYKEHADQIIAKASPGNQLNQYQDIPA
DRNRFVDPDNLTPEVQNELAQFAAHMINSVRRQLGLPPVTVTAGSQEFARLLSTSYKKTHGNTRPSFVYGQPG
VSGHYGVGPHDKTIIEDSAGASGLIRNDDNMYENIGAFNDVHTVNGIKRGIYDSIKYMLFTDHLHGNTYGHAI
NFLRVDKRNPNAPV

> Spy0269-1 / Schmitz 1/177 (serotype 22); SEQ ID NO: 61
DDRASGETKASNTHDDSLPKPETIQEAKATIEAVEKALSQQKAELTELATALTKTTAKINHLKEQQDNEQKAL
TSAQEIYTNTLASSEETLLAQGAEHQRELTATETELHNAQADQHSKETALSEQKASISAETTRAQDLVEQVKT
SEQNIAKLNAMISNPDAITKAAQTANDNTKALSSELEKAKADLENQKAKVKKQLTEELAAQKAALAEKEAELS
RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNNYYKEHADQIIAKASPGNQLNQYQDIPA
DRNRFVDPDNLTPEVQNELAQFAAHMINSVRRQLGLPPVTVTAGSQEFARLLSTSYKKTHGNTRPSFVYGQPG
VSGHYGVGPHDKTIIEDSAGASGLIRNDDNMYENIGAFNDVHTVNGIKRGIYDSIKYMLFTDHLHGNTYGHAI
NFLRVDKRNPNAPV

> Spy0269-1 / Schmitz 1/43 (serotype 22); SEQ ID NO: 62
DDRASGETKASNTHDDSLPKPETIQEAKATIEAVEKALSQQKAELTELATALTKTTAKINHLKEQQDNEQKAL
TSAQEIYTNTLASSEETLLAQGAEHQRELTATETELHNAQADQHSKETALSEQKASISAETTRAQDLVEQVKT
SEQNIAKLNAMISNPDAITKAAQTANDNTKALSSELEKAKADLENQKAKVKKQLTEELAAQKAALAEKEAELS
RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNNYYKEHADQIIAKASPGNQLNQYQDIPA
DRNRFVDPDNLTPEVQNELAQFAAHMINSVRRQLGLPPVTVTAGSQEFARLLSTSYKKTHGNTRPSFVYGQPG
VSGHYGVGPHDKTIIEDSAGASGLIRNDDNMYENIGAFNDVHTVNGIKRGIYDSIKYMLFTDHLHGNTYGHAI
NFLRVDKRNPNAPV

> Spy0269-1 / Schmitz 1/136 (serotype 25); SEQ ID NO: 63
DDRASGETKASNTHDDSLPKPETIQEAKATIDAVEKTLSQQKAELTELATALTKTTAEINHLKEQQDNEQKAL
TSAQEIYTNTLASSEETLLAQGAEHQRELTATETELHNAQADQHSKETALSEQKASISAETTRAQDLVEQVKT
SEQNIAKLNAMISNPDAITKAAQTANDNTKALSSELEKAKADLENQKAKVKKQLTEELAAQKAALAEKEAELS
RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNNYYKEHADQIIAKASPGNQLNQYQDIPA
DRNRFVDPDNLTPEVQNELAQFAAHMINSVRRQLGLPPVTVTAGSQEFARLLSTSYKKTHGNTRPSFVYGQPG
VSGHYGVGPHDKTIIEDSAGASGLIRNDDNMYENIGAFNDVHTVNGIKRGIYDSIKYMLFTDHLHGNTYGHAI
NFLRVDKRNPNAPV

> Spy0269-1 / Schmitz 1/85 (serotype 28); SEQ ID NO: 64
DDRASGETKASNTHDDSLPKPETIQEAKATIDAVEKTLSQQKAELTELATALTKTTAEINHLKEQQDNEQKAL
TSAQEIYTNTLASSEETLLAQGAEHQRELTATETELHNAQADQHSKETALSEQKASISAETTRAQDLVEQVKT
SEQNIAKLNAMISNPDAITKAAQTANDNTKALSSELEKAKADLENQKAKVKKQLTEELAAQKAALAEKEAELS
RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNNYYKEHADQIIAKASPGNQLNQYQDIPA
DRNRFVDPDNLTPEVQNELAQFAAHMINSVRRQLGLPPVTVTAGSQEFARLLSTSYKKTHGNTRPSFVYGQPG
VSGHYGVGPHDKTIIEDSAGASGLIRNDDNMYENIGAFNDVHTVNGIKRGIYDSIKYMLFTDHLHGNTYGHAI
NFLRVDKHNPNAPV

> Spy0269-1 / Schmitz 2/50 (serotype 28); SEQ ID NO: 65
DDRASGETKASNTHDDSLPKPETIQEAKATIDAVEKTLSQQKAELTELATALTKTTAEINHLKEQQDNEQKAL
TSAQEIYTNTLASSEETLLAQGAEHQRELTATETELHNAQVDQHSKETALSEQKASISAETTRAQDLVEQVKT
SEQNIAKLNAMISNPDAITKAAQTANDNTKALSSELEKAKADLENQKAKVKKQLTEELAAQKAALAEKEAELS
RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNNYYKEHADQIIAKASPGNQLNQYQDIPA
DRNRFVDPDNLTPEVQNELAQFAAHMINSVRRQLGLPPVTVTAGSQEFARLLSTSYKKTHGNTRPSFVYGQPG
VSGHYGVGPHDKTIIEDSAGASGLIRNDDNMYENIGAFNDVHTVNGIKRGIYDSIKYMLFTDHLHGNTYGHAI
NFLRVDKRNPNAPV

> Spy0269-1 / Schmitz 1/123 (serotype 49); SEQ ID NO: 66
DDRASGETKASNTHDDSLPKPETIQEAKATIDAVEKTLSQQKAELTELATALTKTTAEINHLKEQQDNEQKAL
TSAQEIYTNTLASSEETLLAQGAEHQRELTATETELHNAQADQHSKETALSEQKASISAETTRAQDLVEQVKT
SEQNIAKLNAMISNPDAITKAAQTANDNTKALSSELEKAKADLENQKAKVKKQLTEELAAQKAALAEKEAELS
RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNNYYKEHADQIIAKASPGNQLNQYQDIPA
DRNRFVDPDNLTPEVQNELAQFAAHMINSVRRQLGLPPVTVTAGSQEFARLLSTSYKKTHGNTRPSFVYGQPG
VSGHYGVGPHDKTIIEDSAGASGLIRNDDNMYENIGAFNDVHTVNGIKRGIYDSIKYMLFTDHLHGNTYGHAI
NFLRVDKRNPNAPV

> Spy0269-1 / Schmitz 1/176 (serotype 83); SEQ ID NO: 67
DDRASGETKASNTHDDSLPKPETIQEAKATIEAVEKTLSQQKAELTELATALTKTTAEINHLKEQQDNEQKAL
TSAQEIYTNTLASSEETLLAQGAEHQRELTATETELHNAQADQHSKETALSEQKASISAETTRAQDLVEQVKT
SEQNIAKLNAMISNPDAITKAAQTANDNTKALSSELEKAKADLENQKAKVKKQLTEELAAQKAALAEKEAELS
RLKSSAPSTQDSIVGNNTMKAPQGYPLEELKKLEASGYIGSASYNNYYKEHADQIIAKASPGNQLNQYQDIPA
DRNRFVDPDNLTPEVQNELAQFAAHMINSVRRQLGLPPVTVTAGSQEFARLLSTSYKKTHGNTRPSFVYGQPG

VSGHYGVGPHDKTIIEDSAGASGLIRNDDNMYENIGAFNDVHTVNGIKRGIYDSIKYMLFTDHLHGNTYGHAI
NFLRVDKRNPNAPV

2. Spy0292

2.1 Full length Spy0292

> Spy0292 / SF370 (serotype 1); SEQ ID NO: 68
MIKRLISLVVIALFFAASTVSGEEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKG
KLNWDSPVTISNYPYELTTNYTISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQL
RQWGISDAKVVNSTGLTNHFLGANTYPNTEPDDENCFCATDLAIIARHLLLEFPEVLKLSSKSSTIFAGQTIY
SYNYMLKGMPCYREGVDGLFVGYSKKAGASFVATSVENQMRVITVVLNADQSHEDDLAIFKTTNQLLQYLLIN
FQKVQLIENNKPVKTLYVLDSPEKTVKLVAQNSLFFIKPIHTKTKNTVHITKKSSTMIAPLSKGQVLGRATLQ
DKHLIGQGYLDTPPSINLILQKNISKSFFLKVWWNRFVRYVNTSL

2.2 Antigenic fragment Spy0292-1

> Spy0292-1 / SF370 (serotype 1); SEQ ID NO: 2
EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDAKVVNSTGLTNHFLG
ANTYPNTEPDDENCFC

2.3 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0292-1 / Schmitz 1/39 (serotype 12); SEQ ID NO: 69
EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDAKVVNSTGLTNHFLG
ANTYPNTEPDDENCFC

> Spy0292-1 / Schmitz 1/55 (serotype 118); SEQ ID NO: 70
EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDTKVVNSTGLTNHFLG
ANTYPNTEPDDENCFC

> Spy0292-1 / Schmitz 1/56 (serotype 28); SEQ ID NO: 71
EEYSVTAKHAIAVDLESGKVLYEKDTKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDAKVVNSTGLTNHFLG
ANTYPNTEPDDENCFC

> Spy0292-1 / Schmitz 1/74 (serotype 3); SEQ ID NO: 72
EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDAKVVNSTGLTNHFLG
ANTYPNTEPDDENCFC

> Spy0292-1 / Schmitz 1/76 (serotype 22); SEQ ID NO: 73
EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDAKVVNSTGLTNHFLG
ANTYPNTEPDDENCFC

> Spy0292-1 / Schmitz 1/92 (serotype 11); SEQ ID NO: 74
EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDAKVVNSTGLTNHFLG
ANTYPNTEPDDENCFC

> Spy0292-1 / Schmitz 1/94 (serotype 1); SEQ ID NO: 75
EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDAKVVNSTGLTNHFLG
ANTYPNTEPDDENCFC

> Spy0292-1 / Schmitz 1/142 (serotype 83); SEQ ID NO: 76

EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDAKVVNSTGLTNHFLG
ANTYPNTEPDDENCFC

> Spy0292-1 / Schmitz 1/144 (serotype 76); SEQ ID NO: 77
EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDAKVVNSTGLTNHFLG
ANTYPNTEPDDENCFC

> Spy0292-1 / Schmitz 1/194 (serotype 44); SEQ ID NO: 78
EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDAKVVNSTGLTNHFLG
ANTYPNTEPDDENCFC

2.4 Antigenic fragment Spy0292-3

> Spy0292-3 / SF370 (serotype 1); SEQ ID NO: 3
EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDAKVVNSTGLTNHFLG
ANTYPNTEPDDENCFCATDLAIIARHLLLEFPEVLKLSSKSSTIFAGQTIYSYNYMLKGMPCYREGVDGLFVG
YSKKAGASFVATSVENQMRVITVVLNADQSHEDDLAIFKTTNQLLQYLLINFQKVQLIE

2.5 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0292-3 / Schmitz 1/39 (serotype 12); SEQ ID NO: 79
EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDAKVVNSTGLTNHFLG
ANTYPNTEPDDENCFCATDLAIIARHLLLEFPEVLKLSSKSSTIFDGQTIYSYNYMLKGMPCYREGVDGLFVG
YSKKAGASFVATSVENQMRVITVVLNADQSHEDDLAIFKTTNQLLQYLLINFQKVQLIE

> Spy0292-3 / Schmitz 1/55 (serotype 118); SEQ ID NO: 80
EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDTKVVNSTGLTNHFLG
ANTYPNTEPDDENCFCATDLAIIARHLLLEFPEVLKLSSKSSTIFDGQTIYSYNYMLKGMPCYREGVDGLFVG
YSKKAGASFVATSVENQMRVITVVLNADQSHEDDLAIFKTTNQLLQYLLINFQKVQLIE

> Spy0292-3 / Schmitz 1/56 (serotype 28); SEQ ID NO: 81
EEYSVTAKHAIAVDLESGKVLYEKDTKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDAKVVNSTGLTNHFLG
ANTYPNTEPDDENCFCATDLAIIARHLLLEFPEVLKLSSKSSTIFDGQTIYSYNYMLKGMPCYREGVDGLFVG
YSKKAGASFVATSVENQMRVITVVLNADQSHEDDLAIFKTTNQLLQYLLINFQKVQLIE

> Spy0292-3 / Schmitz 1/74 (serotype 3); SEQ ID NO: 82
EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDAKVVNSTGLTNHFLG
ANTYPNTEPDDENCFCATDLAIIARHLLLEFPEVLKLSSKSSTIFAGQTIYSYNYMLKGMPCYREGVDGLFVG
YSKKAGASFVATSVENQMRVITVVLNADQSHEDDLAIFKTTNQLLQYLLINFQKVQLIE

> Spy0292-3 / Schmitz 1/76 (serotype 22); SEQ ID NO: 83
EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDAKVVNSTGLTNHFLG
ANTYPNTEPDDENCFCATDLAIIARHLLLEFPEVLKLSSKSSTIFDGQTIYSYNYMLKGMPCYREGVDGLFVG
YSKKAGASFVATSVENQMRVITVVLNADQSHEDDLAIFKTTNQLLQYLLINFQKVQLIE

> Spy0292-3 / Schmitz 1/92 (serotype 11); SEQ ID NO: 84
EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDAKVVNSTGLTNHFLG
ANTYPNTEPDDENCFCATDLAIIARHLLLEFPEVLKLSSKSSTIFDGQTIYSYNYMLKGMPCYREGVDGLFIG
YSKKAGASFVATSVENQMRVITVVLNADQSHEDDLAIFKTTNQLLQYLLINFQKVQLIE

> Spy0292-3 / Schmitz 1/94 (serotype 1); SEQ ID NO: 85
EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDAKVVNSTGLTNHFLG
ANTYPNTEPDDENCFCATDLAIIARHLLLEFPEVLKLSSKSSTIFAGQTIYSYNYMLKGMPCYREGVDGLFVG
YSKKAGASFVATSVENQMRVITVVLNADQSHEDDLAIFKTTNQLLQYLLINFQKVQLIE

> Spy0292-3 / Schmitz 1/142 (serotype 83); SEQ ID NO: 86
EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDAKVVNSTGLTNHFLG
ANTYPNTEPDDENCFCATDLAIIARHLLLEFPEVLKLSSKSSTIFDGQTIYSYNYMLKGMPCYREGVDGLFVG
YSKKAGASFVATSVENQMRVITVVLNADQSHEDDLAIFKTTNQLLQYLLINFQKVQLIE

> Spy0292-3 / Schmitz 1/144 (serotype 76); SEQ ID NO: 87
EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDAKVVNSTGLTNHFLG
ANTYPNTEPDDENCFCATDLAIIARHLLLEFPEVLKLSSKSSTIFDGQTIYSYNYMLKGMPCYREGVDGLFVG
YSKKAGASFVATSVENQMRVITVVINADQSHEDDLAIFKTTNQLLQYLLINFQKVQLIE

> Spy0292-3 / Schmitz 1/194 (serotype 44); SEQ ID NO: 88
EEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELTTNYT
ISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDAKVVNSTGLTNHFLG
ANTYPNTEPDDENCFCATDLAIIARHLLLEFPEVLKLSSKSSTIFAGQTIYSYNYMLKGMPCYREGVDGLFVG
YSKKAGASFVATSVENQMRVITVVLNADQSHEDDLAIFKTTNQLLQYLLINFQKVQLIE

3. Spy0416A

3.1 Full length Spy0416A

> Spy0416A / SF370 (serotype 1); SEQ ID NO: 89
ADELSTMSEPTITNHAQQQAQHLTNTELSSAESKSQDTSQITLKTNREKEQSQDLVSEPTTTELADTDAASMA
NTGSDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQGKVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLA
RQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDEDWENFEFDAEAEPKAIKKHKIYRPQSTQAPKET
VIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKEAAATGERFLGIAPEAQVMFMRVFANDIMGSAE
SLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPD
YGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLNHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKE
STDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGALGVLIFNNKPGQSNRSMRLTANGMGIPSAFISHEF
GKAMSQLNGNGTGSLEFDSVVSKAPSQKGNEMNHFSNWGLTSDGYLKPDITAPGGDIYSTYNDNHYGSQTGTS
MASPQIAGASLLVKQYLEKTQPNLPKEKIADIVKNLLMSNAQIHVNPETKTTTSPRQQGAGLLNIDGAVTSGL
YVTGKDNYGSISLGNITDTMTFDVTVHNLSNKDKTLRYDTELLTDHVDPQKGRFTLTSHSLKTYQGGEVTVPA
NGKVTVRVTMDVSQFTKELTKQMPNGYYLEGFVRFRDSQDDQLNRVNIPFVGFKGQFENLAVAEESIYRLKSQ
GKTGFYFDESGPKDDIYVGKHFTGLVTLGSE

3.2 Antigenic fragment Spy0416A-1

> Spy0416A-1 / SF370 (serotype 1); SEQ ID NO: 4
ADELSTMSEPTITNHAQQQAQHLTNTELSSAESKSQDTSQITLKTNREKEQSQDLVSEPTTTELADTDAASMA
NTGSDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQGKVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLA
RQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDEDWENFEFDAEAEPKAIKKHKIYRPQSTQAPKET
VIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKEAAATGERFLGIAPEAQVMFMRVFANDIMGSAE
SLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPD
YGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLNHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKE
STDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGALGVLIFNNKPGQSNRSMRLTANGMGIPSAFISHEF
GKAMSQLNGNGTGSLEFDSVVSKAPSQKGNEMNHFSNWGLTSDGYLKPDITAPGGDIYSTYNDNHYGSQTGTS
MASPQIAGASLLVKQYLEKTQPNLPKEKIADIVKNLLMSNAQIHVNPETKTTTSPRQQGA

3.3 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0416A-1 / Schmitz 1/7 (serotype 4); SEQ ID NO: 90
ADELTTTSEPTITNHAQQQAQHLTNTELSSAESQSPDTSQITPKTNREKEQPQGLVSEPTTTELADTDAASMA
NTGPDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQGKVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLA

RQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFGDFDEDWENFEFDAEPKAIKKNKIYRPQSTQAPKETVI
KTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKEAAATGERFLGIAPEAQVMFMRVFANDVMGSAESL
FIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYG
LVGSPSTGRTPTSVAAINSKWVIQRLMTAKELENRADLNHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKEST
DAGYKAQDVKDKIALIERDPNKTYDEMIALAKKHGALGVLIFNNKPGQSNRSMRLTANGMGIPSAFISHEFGK
AMSQLNGNGTGSLEFDSVVSKAPSQKGNEMNHFSNWGLTSDGYLKPDITAPGGDIYSTYNDNHYGSQTGTSMA
SPQIAGASLLVKQYLEKTQPNLPKEKIADIVKNLLMSNAQIHVNPETKTTTSPRQQGA

> Spy0416A-1 / Schmitz 1/39 (serotype 12); SEQ ID NO: 91
ADELTTTSEPTITNHTQQQAQHLTNTELSSAESKPQDTSQITLKTNREKEQPQGLVSEPTTTELADTDAAPMA
NTGPDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQGKVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLA
RQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDEDWENFEFDAEAEPKAIKKHKIYRPQSTQAPKET
VIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKEAAATGERFLGIAPEAQVMFMRVFANDVMGSAE
SLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPD
YGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLNHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKE
STDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGALGVLIFNNKPGQSNRSMRLTANGMGIPSAFISHEF
GKAMSQLNGNGTGSLEFDSVVSKAPSQKGNEMNHFSNWGLTSDGYLKPDITAPGGDIYSTYNDNHYGSQTGTS
MASPQIAGASLLVKQYLEKTQPNLPKEKIADIVKNLLMSNAQIHVNPETKTTTSPRQQGA

> Spy0416A-1 / Schmitz 1/55 (serotype 118); SEQ ID NO: 92
ADELTTTSEPTITNHAQQQAPPLTNTELSSAESQPQDTSQVTPETNREKEQPQGLVSEPTTTELADTDAAPMA
NTGSDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQGKVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLA
RQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDEDWENFEFDAEAEPKAIKKHKIYRPQSTQAPKET
VIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKEAAATGERFLGIAPEAQVMFMRVFANDVMGSAE
SLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPD
YGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLNHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKE
STDAGYNAQNVKGKIALIERDPNKTYDEMIALAKKHGALGVLIFNNKPGQSNRSMRLTANGMGIPSAFISHEF
GKAMSQLNGNGTGSLEFDSVVSKAPSQKGNEMNHFSNWGLTSDGYLKPDITAPGGDIYSTYNDNHYGSQTGTS
MASPQIAGASLLVKQYLEKTQPNLPKEKIADIVKNLLMSNAQIHVNPETKTTTSPRQQGA

> Spy0416A-1 / Schmitz 1/56 (serotype 28); SEQ ID NO: 93
ADELTTTSEPTITNHAQQQAPPLTNTELSSAESQPQDTSQVTPETNREKEQPQGLVSEPTTTELADTDAAPMA
NTGSDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQGKVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLA
RQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDEDWENFEFDAEAEPKAIKKHKIYRPQSTQAPKET
VIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKEAAATGERFLGIAPEAQVMFMRVFANDVMGSAE
SLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPD
YGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLNHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKE
STDAGYNAQNVKGKIALIERDPNKTYDEMIALAKKHGALGVLIFNNKPGQSNRSMRLTANGMGIPSAFISHEF
GKAMSQLNGNGTGSLEFDSVVSKAPSQKGNEMNHFSNWGLTSDGYLKPDITAPGGDIYSTYNDNHYGSQTGTS
MASPQIAGASLLVKQYLEKTQPNLPKEKIADIVKNLLMSNAQIHVNPETKTTTSPRQQGA

> Spy0416A-1 / Schmitz 1/94 (serotype 1); SEQ ID NO: 94
ADELSTMSEPTITNHAQQQAQHLTNTELSSAESKSQDTSQITLKTNREKEQSQDLVSEPTTTELADTDAASMA
NTGSDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQGKVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLA
RQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDEDWENFEFDAEAEPKAIKKHKIYRPQSTQAPKET
VIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKEAAATGERFLGIAPEAQVMFMRVFANDIMGSAE
SLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPD
YGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLNHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKE
STDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGALGVLIFNNKPGQSNRSMRLTANGMGIPSAFISHEF
GKAMSQLNGNGTGSLEFDSVVSKAPSQKGNEMNHFSNWGLTSDGYLKPDITAPGGDIYSTYNDNHYGSQTGTS
MASPQIAGASLLVKQYLEKTQPNLPKEKIADIVKNLLMSNAQIHVNPETKTTTSPRQQGA

> Spy0416A-1 / Schmitz 1/253 (serotype 49); SEQ ID NO: 95
ADELTTTSEPTITNHAQQQAQPLTNTELSSAESQSPDISQVTPETNREKEQPQGLVSEPTTTELADTDAAPMA
NTGPDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQGKVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLA
RQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDEDWENFEFDADAEPKAIKKHKIYRPQSTQAPKET
VIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKEAAATGERFLGIAPEAQVMFMRVFANDVMGSAE
SLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPD
YGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKGLENRADLNHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKE
STDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGALGLLIFNNKSGQSNRSMRLTANGMGIPSAFISHEF

GKAMSQLNGNGTGSLEFDSVVSKAPSQKGNEMNHFSNWGLTSDGYLKPDITAPGGDIYSTYNDNHYGSQTGTS
MASPQIAGASLLVKQYLEKTQPNLPKEKIADIVKNLLMSNAQIHVNPETKTTTSPRQQGA

> Spy0416A-1 / Schmitz 1/174 (serotype 6); SEQ ID NO: 96
ADELTTTSEPTITNHAQQQAQHLTNTELSSAESKPQDTSQITPKTNREKEQSQDLVSEPTTTELADTDAASMA
NTGPDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQGKVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLA
RQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDEDWENFEFDAEAEPKAIKKHKIYRPQSTQAPKET
VIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKEAAATGERFLGIAPEAQVMFMRVFANDVMGSAE
SLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPD
YGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLNHGKAIYSESVDFKNIKDSLGYDKSHQFAYVKE
STDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGALGVLIFNNKPGQSNRSMRLTSNGMGIPSAFISHEF
GKAMSQLNGNGTGSLEFDSVVSKAPSQKGNEMNHFSNWGLTSDGYLKPDITAPGGDIYSTYNDNHYGSQTGTS
MASPQIAGASLLVKQYLEKTQPNLPKEKIADIVKNLLMSNAQIHVNPETKTTTSPRQQGA

> Spy0416A-1 / Schmitz 1/176 (serotype 83); SEQ ID NO: 97
ADELTTTSEPTITNHTQQQAQHLTNTELSSAESKPQDTSQITLKTNREKEQPQGLVSEPTTTELADTDAAPMA
NTGPDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQGKVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLA
RQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDEDWENFEFDAEAEPKAIKKHKIYRPQSTQAPKET
VIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKEAAATGERFLGIAPEAQVMFMRVFANDVMGSAE
SLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPD
YGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLNHGKAIYSESVDFKNIKDSLGYDKSHQFAYVKE
STDAGYKAQDVKGKIALIERDPNKTYDEMIALAKKHGALGVLIFNNKPGQSNRSMRLTANGMGIPSAFISHEF
GKAMSQLNGNGTGSLEFDSVVSKAPSQKGNEMNHFSNWGLTSDGYLKPDITAPGGDIYSTYNDNHYGSQTGTS
MASPQIAGASLLVKQYLEKTQPNLPKEKIADIVKNLLMSNAQIHVNPETKTTTSPRQQGA

> Spy0416A-1 / Schmitz 1/234 (serotype 44); SEQ ID NO: 98
ADELSTMSEPTITNHAQQQAQHLTNTELSSAESKSQDTSQITPKTNREKEQSQDLVSEPTTTELADTDAASMA
NTGSDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQGKVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLA
RQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDEDWENFEFDADAEPKAIKKHKIYRPQSTQAPKET
VIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKEAAATGERFLGIAPEAQVMFMRVFANDVMGSAE
SLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPD
YGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLNHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKE
STDAGYKAQDVKDKIALIERDPNKTYDEMIALAKKHGALGVLIFNNKPGQSNRSMRLTANGMGIPSAFISHEF
GKAMSQLNGNGTGSLEFDSVVSKAPSQKGNEMNHFSNWGLTSDGYLKPDITAPGGDIYSTYNDNHYGSQTGTS
MASPQIAGASLLVKQYLEKTQPNLPKEKIADIVKNLLMSNAQIHVNPETKTTTSPRQQGA

> Spy0416A-1 / Schmitz 1/22 (serotype 4); SEQ ID NO: 99
ADELTTTSEPTITNHAQQQAQHLTNTELSSAESQSPDTSQITPKTNREKEQPQGLVSEPTTTELADTDAASMA
NTGPDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQGKVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLA
RQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFGDFDEDWENFEFDAEPKAIKKNKIYRPQSTQAPKETVI
KTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKEAAATGERFLGIAPEAQVMFMRVFANDVMGSAESL
FIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYG
LVGSPSTGRTPTSVAAINSKWVIQRLMTAKELENRADLNHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKEST
DAGYKAQDVKDKIALIERDPNKTYDEMIALAKKHGALGVLIFNNKPGQSNRSMRLTANGMGIPSAFISHEFGK
AMSQLNGNGTGSLEFDSVVSKAPSQKGNEMNHFSNWGLTSDGYLKPDITAPGGDIYSTYNDNHYGSQTGTSMA
SPQIAGASLLVKQYLEKTQPNLPKEKIADIVKNLLMSNAQIHVNPETKTTTSPRQQGA

3.4 Antigenic fragment Spy0416A-6

> Spy0416A-6 / SF370 (serotype 1); SEQ ID NO: 5
AVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDED
WENFEFDAEAEPKAIKKHKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKE
AAATGERFLGIAPEAQVMFMRVFANDIMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIE
KAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLN
HGKAIYSESVDFKDIKDSL

3.5 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0416A-6 / Schmitz 1/7 (serotype 4); SEQ ID NO: 100
AVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFGDFDED

WENFEFDAEPKAIKKNKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKEAA
ATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIEKA
KKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTAKELENRADLNHG
KAIYSESVDFKDIKDSL

> Spy0416A-6 / Schmitz 1/39 (serotype 12); SEQ ID NO: 101
AVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDED
WENFEFDAEAEPKAIKKHKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKE
AAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIE
KAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLN
HGKAIYSESVDFKDIKDSL

> Spy0416A-6 / Schmitz 1/55 (serotype 118); SEQ ID NO: 102
AVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDED
WENFEFDAEAEPKAIKKHKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKE
AAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIE
KAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLN
HGKAIYSESVDFKDIKDSL

> Spy0416A-6 / Schmitz 1/56 (serotype 28); SEQ ID NO: 103
AVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDED
WENFEFDAEPKAIKKHKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKEAA
ATGERFLGIAPETQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIEKA
KKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLNHG
KAIYSESVDFKDIKDSL

> Spy0416A-6 / Schmitz 1/94 (serotype 1); SEQ ID NO: 104
AVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDED
WENFEFDAEAEPKAIKKHKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKE
AAATGERFLGIAPEAQVMFMRVFANDIMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIE
KAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLN
HGKAIYSESVDFKDIKDSL

> Spy0416A-6 / Schmitz 1/253 (serotype 49); SEQ ID NO: 105
AVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDED
WENFEFDADAEPKAIKKHKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKE
AAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIE
KAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKGLENRADLN
HGKAIYSESVDFKDIKDSL

> Spy0416A-6 / Schmitz 1/174 (serotype 6); SEQ ID NO: 106
AVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDED
WENFEFDAEAEPKAIKKHKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKE
AAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIE
KAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLN
HGKAIYSESVDFKNIKDSL

> Spy0416A-6 / Schmitz 1/176 (serotype 83); SEQ ID NO: 107
AVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDED
WENFEFDAEAEPKAIKKHKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKE
AAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIE
KAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLN
HGKAIYSESVDFKNIKDSL

> Spy0416A-6 / Schmitz 1/234 (serotype 44); SEQ ID NO: 108
AVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDED
WENFEFDADAEPKAIKKHKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKE
AAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIE
KAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADLN
HGKAIYSESVDFKDIKDSL

> Spy0416A-6 / Schmitz 1/22 (serotype 4); SEQ ID NO: 109
AVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFGDFDED
WENFEFDAEPKAIKKNKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSKEAA
ATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAIEKA
KKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTAKELENRADLNHG
KAIYSESVDFKDIKDSL

3.6 Antigenic fragment Spy0416A-7

> Spy0416A-7 / SF370 (serotype 1); SEQ ID NO: 6
SQITLKTNREKEQSQDLVSEPTTTELADTDAASMANTGSDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQG
KVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDF
DEDWENFEFDAEAEPKAIKKHKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGN
SKEAAATGERFLGIAPEAQVMFMRVFANDIMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLME
AIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRA
DLNHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKESTDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGA
LGVLIFNNKPGQSNRSMRLTANGMGIPSAFISHEFGKAMSQLNGNGTGS

3.7 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0416A-7 / Schmitz 1/7 (serotype 4); SEQ ID NO: 110
SQITPKTNREKEQPQGLVSEPTTTELADTDAASMANTGPDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQG
KVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFGDF
DEDWENFEFDAEPKAIKKNKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSK
EAAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAI
EKAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTAKELENRADL
NHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKESTDAGYKAQDVKDKIALIERDPNKTYDEMIALAKKHGALG
VLIFNNKPGQSNRSMRLTANGMGIPSAFISHEFGKAMSQLNGNGTGS

> Spy0416A-7 / Schmitz 1/39 (serotype 12); SEQ ID NO: 111
SQITLKTNREKEQPQGLVSEPTTTELADTDAAPMANTGPDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQG
KVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDF
DEDWENFEFDAEAEPKAIKKHKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGN
SKEAAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLME
AIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRA
DLNHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKESTDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGA
LGVLIFNNKPGQSNRSMRLTANGMGIPSAFISHEFGKAMSQLNGNGTGS

> Spy0416A-7 / Schmitz 1/55 (serotype 118); SEQ ID NO: 112
SQVTPETNREKEQPQGLVSEPTTTELADTDAAPMANTGSDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQG
KVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDF
DEDWENFEFDAEAEPKAIKKHKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGN
SKEAAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLME
AIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRA
DLNHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKESTDAGYNAQNVKGKIALIERDPNKTYDEMIALAKKHGA
LGVLIFNNKPGQSNRSMRLTANGMGIPSAFISHEFGKAMSQLNGNGTGS

> Spy0416A-7 / Schmitz 1/56 (serotype 28); SEQ ID NO: 113
SQITPKINREKEQPQGLVSEPTTTELADTDAAPMANTGPDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQG
KVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDF
DEDWENFEFDAEPKAIKKHKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSK
EAAATGERFLGIAPETQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAI
EKAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRADL
NHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKESTDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGALG
VLIFNNKPGQSNRSMRLTANGMGIPSAFISHEFGKAMSQLNGNGTGS

> Spy0416A-7 / Schmitz 1/94 (serotype 1); SEQ ID NO: 114
SQITLKTNREKEQSQDLVSEPTTTELADTDAASMANTGSDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQG
KVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDF

DEDWENFEFDAEAEPKAIKKHKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGN
SKEAAATGERFLGIAPEAQVMFMRVFANDIMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLME
AIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRA
DLNHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKESTDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGA
LGVLIFNNKPGQSNRSMRLTANGMGIPSAFISHEFGKAMSQLNGNGTGS

> Spy0416A-7 / Schmitz 1/253 (serotype 49); SEQ ID NO: 115
SQVTPETNREKEQPQGLVSEPTTTELADTDAAPMANTGPDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQG
KVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDF
DEDWENFEFDADAEPKAIKKHKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGN
SKEAAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLME
AIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKGLENRA
DLNHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKESTDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGA
LGLLIFNNKSGQSNRSMRLTANGMGIPSAFISHEFGKAMSQLNGNGTGS

> Spy0416A-7 / Schmitz 1/174 (serotype 6); SEQ ID NO: 116
SQITPKTNREKEQSQDLVSEPTTTELADTDAASMANTGPDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQG
KVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDF
DEDWENFEFDAEAEPKAIKKHKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGN
SKEAAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLME
AIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRA
DLNHGKAIYSESVDFKNIKDSLGYDKSHQFAYVKESTDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGA
LGVLIFNNKPGQSNRSMRLTSNGMGIPSAFISHEFGKAMSQLNGNGTGS

> Spy0416A-7 / Schmitz 1/176 (serotype 83); SEQ ID NO: 117
SQITLKTNREKEQPQGLVSEPTTTELADTDAAPMANTGPDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQG
KVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDF
DEDWENFEFDAEAEPKAIKKHKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGN
SKEAAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLME
AIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRA
DLNHGKAIYSESVDFKNIKDSLGYDKSHQFAYVKESTDAGYKAQDVKGKIALIERDPNKTYDEMIALAKKHGA
LGVLIFNNKPGQSNRSMRLTANGMGIPSAFISHEFGKAMSQLNGNGTGS

> Spy0416A-7 / Schmitz 1/234 (serotype 44); SEQ ID NO: 118
SQITPKTNREKEQSQDLVSEPTTTELADTDAASMANTGSDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQG
KVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDF
DEDWENFEFDADAEPKAIKKHKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGN
SKEAAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLME
AIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRA
DLNHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKESTDAGYKAQDVKDKIALIERDPNKTYDEMIALAKKHGA
LGVLIFNNKPGQSNRSMRLTANGMGIPSAFISHEFGKAMSQLNGNGTGS

> Spy0416A-7 / Schmitz 1/22 (serotype 4); SEQ ID NO: 119
SQITPKTNREKEQPQGLVSEPTTTELADTDAASMANTGPDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQG
KVVAVIDTGIDPAHQSMRISDVSTAKVKSKEDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFGDF
DEDWENFEFDAEPKAIKKNKIYRPQSTQAPKETVIKTEETDGSHDIDWTQTDDDTKYESHGMHVTGIVAGNSK
EAAATGERFLGIAPEAQVMFMRVFANDVMGSAESLFIKAIEDAVALGADVINLSLGTANGAQLSGSKPLMEAI
EKAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTAKELENRADL
NHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKESTDAGYKAQDVKDKIALIERDPNKTYDEMIALAKKHGALG
VLIFNNKPGQSNRSMRLTANGMGIPSAFISHEFGKAMSQLNGNGTGS

3.8 Full length Spy0416B

> Spy0416B / SF370 (serotype 1); SEQ ID NO: 56
HVDPQKGRFTLTSHSLKTYQGGEVTVPANGKVTVRVTMDVSQFTKELTKQMPNGYYLEGFVRFRDSQDDQLNR
VNIPFVGFKGQFENLAVAEESIYRLKSQGKTGFYFDESGPKDDIYVGKHFTGLVTLGSETNVSTKTISDNGLH
TLGTFKNADGKFILEKNAQGNPVLAISPNGDNNQDFAAFKGVFLRKYQGLKASVYHASDKEHKNPLWVSPESF
KGDKNFNSDIRFAKSTTLLGTAFSGKSLTGAELPDGHYHYVVSYYPDVVGAKRQEMTFDMILDRQKPVLSQAT
FDPETNRFKPEPLKDRGLAGVRKDSVFYLERKDNKPYTVTINDSYKYVSVEDNKTFVERQADGSFILPLDKAK
LGDFYYMVEDFAGNVAIAKLGDHLPQTLGKTPIKLKLTDGNYQTKETLKDNLEMTQSDTGLVTNQAQLAVVHR
NQPQSQLTKMNQDFFISPNEDGNKDFVAFKGLKNNVYNDLTVNVYAKDDHQKQTPIWSSQAGASVSAIESTAW

YGITARGSKVMPGDYQYVVTYRDEHGKEHQKQYTISVNDKKPMITQGRFDTINGVDHFTPDKTKALDSSGIVR
EEVFYLAKKNGRKFDVTEGKDGITVSDNKVYIPKNPDGSYTISKRDGVTLSDYYYLVEDRAGNVSFATLRDLK
AVGKDKAVVNFGLDLPVPEDKQIVNFTYLVRDADGKPIENLEYYNNSGNSLILPYGKYTVELLTYDTNAAKLE
SDKIVSFTLSADNNFQQVTFKITMLATSQITAHFDHLLPEGSRVSLKTAQDQLIPLEQSLYVPKAYGKTVQEG
TYEVVVSLPKGYRIEGNTKVNTLPNEVHELSLRLVKVGDASDSTGDHKVMSKNNSQALTASATPTKSTTSATA
KALPST

4. Spy0872

4.1 Full length Spy0872

> Spy0872 / SF370 (serotype 1); SEQ ID NO: 120
DQVDVQFLGVNDFHGALDNTGTAYTPSGKIPNAGTAAQLGAYMDDAEIDFKQANQDGTSIRVQAGDMVGASPA
NSALLQDEPTVKVFNKMKFEYGTLGNHEFDEGLDEFNRIMTGQAPDPESTINDITKQYEHEASHQTIVIANVI
DKKTKDIPYGWKPYAIKDIAINDKIVKIGFIGVVTTEIPNLVLKQNYEHYQFLDVAETIAKYAKELQEQHVHA
IVVLAHVPATSKDGVVDHEMATVMEKVNQIYPEHSIDIIFAGHNHQYTNGTIGKTRIVQALSQGKAYADVRGT
LDTDTNDFIKTPSANVVAVAPGIKTENSDIKAIINHANDIVKTVTERKIGTATNSSTISKTENIDKESPVGNL
ATTAQLTIAKKTFPTVDFAMTNNGGIRSDLVVKNDRTITWGAAQAVQPFGNILQVIQMTGQHIYDVLNQQYDE
NQTYFLQMSGLTYTYTDNDPKNSDTPFKIVKVYKDNGEEINLTTTYTVVVNDFLYGGGDGFSAFKKAKLIGAI
NTDTEAFITYIITNLEASGKTVNATIKGVKNYVTSNLESSTKVNSAGKHSIISKVFRNRDGNTVSSEVISDLLT
STENTNNSLGKKETTTNKNTISSSTLPIT

4.2 Antigenic fragment Spy0872-2

> Spy0872-2 / SF370 (serotype 1); SEQ ID NO: 7
AIINHANDIVKTVTERKIGTATNSSTISKTENIDKESPVGNLATTAQLTIAKKTFPTVDFAMTNNGGIRSDLV
VKNDRTITWGAAQAVQPFGNILQVIQMTGQHIYDVLNQQYDENQTYFLQMSGLTYTYTDNDPKNSDTPFKIVK
VYKDNGEEINLTTTYTVVVNDFLYGGGDGFSAFKKAKLIGAINTDTEAFITYITNLEASGKTVNATIKGVKNY
VTSNLESSTKVNSAGKHSIISKVFRNRDGNTVSSEVISDLLTSTENTNNSLGKKETTTNKNTISSSTLPIT

4.3 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0872-2 / Schmitz 1/7 (serotype 4); SEQ ID NO: 121
AIINHANDIVKTVTERKIGTATNSSTISKTENIDKESPVGNLVTTAQLTIAKKTFPTVDFAMTNNGGIRSDLV
VKNDRTITWEAAQAVQPFGNILQVIQMTGQHIYDVLNQQYDENQTYFLQMSGLTYTYTDNDPKNSDTPFKIVK
VYKDNGEEINLTTTYTVVVNDFLYGGGDGFSAFKKAKLIGAINTDTEAFITYITNLEASGKTVNATIKGVKNY
VTSNLESSTKVNSAGKHSIIIISKVFRNRDGNIVSSEIISDLLTSTENTNNSFGKKEITTNKNTISNSTLPIT

> Spy0872-2 / Schmitz 1/39 (serotype 12); SEQ ID NO: 122
AIINHANDIVKTVTERKIGTATNSSTISKTENIDKESPVGNLVTTAQLTIAKKTFPTVDFAMTNNGGIRSDLV
VKNDRTITWGAAQAVQPFGNILQVIQMTGQHIYDVLNQQYDENQTYFLQMSGLTYTYTDNDPKNSDTPFKIVK
VYKDNGEEINLTTTYTVVVNDFLYGGGDGFSAFKKAKLIGAINTDTEAFITYITNLEASGKTVNATIKGVKNY
VTSNLESSTKVNSAGKHSIISKVFRNRDGNIVSSEIISDLLTSTENTNNSLGKKETTTNKNTISSSTLPIT

> Spy0872-2 / Schmitz 1/55 (serotype 118); SEQ ID NO: 123
AIINHANDIVKTVTERKIGTATNSSTISKTENIDKESPVGNLVTTAQLTIAKKTFPTVDFAMTNNGGIRSDLV
VKNDRTITWGAAQAVQPFGNILQVIQMTGQHIYDVLNQQYDENQTYFLQMSGLTYTYTDNDPKNSDIPFKIVK
VYKDNGEEINLTTTYTVVVNDFLYGGGDGFSAFKKAKLIGAINTDTEAFITYITNLEASGKTVNATIKGVKNY
VTSNLESSTKVNSAGKHSIISKVFRNRDGNIVSSEVISDLLTSTENTNNSLGKKETTTNKNTISSSTLPIT

> Spy0872-2 / Schmitz 1/56 (serotype 28); SEQ ID NO: 124
AIINHANDIVKTVTERKIGTATNSSTISKTENIDKESPVGNLVTTAQLTIAKKTFPTVDFAMTNNGGIRSDLV
VKNDRTITWGAAQAVQPFGNILQVIQMTGQHIYDVLNQQYDENQTYFLQMSGLTYTYTDNDPKNSDTPFKIVK
VYKDNGEEINLTTTYTVVVNDFLYGGGDGFSAFKKAKLIGAINTDTEAFITYITNLEASGKTVNATIKGVKNY
VTSNLESSTKVNSAGKHSIISKVFRNRDGNIVSSEIISDLLTSTENTNNSLGKKETTTNKNTISSSTLPIT

> Spy0872-2 / Schmitz 1/94 (serotype 1); SEQ ID NO: 125
AIINHANDIVKTVTERKIGTATNSSTISKTENIDKESPVGNLATTAQLTIAKKTFPTVDFAMTNNGGIRSDLV
VKNDRTITWGAAQAVQPFGNILQVIQMTGQHIYDVLNQQYDENQTYFLQMSGLTYTYTDNDPKNSDTPFKIVK
VYKDNGEEINLTTTYTVVVNDFLYGGGDGFSAFKKAKLIGAINTDTEAFITYITNLEASGKTVNATIKGVKNY

VTSNLESSTKVNSAGKHSIISKVFRNRDGNTVSSEVISDLLTSTENTNNSLGKKETTTNKNTISSSTLPIT

> Spy0872-2 / Schmitz 1/253 (serotype 49); SEQ ID NO: 126
AIINHANDIVKTVTERKIGTATNSSTISKTENIDKESPVGNLVTTAQLTIAKKTFPTVDFAMTNNGGIRSDLV
VKNDRTITWGAAQAVQPFGNILQVIQMTGQHIYDVLNQQYDENQTYFLQMSGLTFTYTDNDPKNSDTPFKIVK
VYKDNGEEINLTTTYTVVVNDFLYGGGDGFSAFKKAKLIGAINTDTEAFITYITNLEASGKTVNATIKGVKNY
VTSNLESSTKVNSAGKHSIISKVFRNRDGNIVSSEIISDLLTSTENTNNSLGKKETTTNKNTISSSTLPIT

> Spy0872-2 / Schmitz 1/176 (serotype 83); SEQ ID NO: 127
AIINHANDIVKTVTERKIGTATNSSTISKTENIDKESPVGNLVTTAQLTIAKKTFPTVDFAMTNNGGIRSDLV
VKNDRTITWGAAQAVQPFGNILQVIQMTGQHIYDVLNQQYDENQTYFLQMSGLTYTYTDNDPKNSDTPFKIVK
VYKDNGEEINLTTTYTVVVNDFLYGGGDGFSAFKKAKLVGAINTDTEAFITYITNLQASGKTVNATIKGVKNY
VTSNLERSTKINSAGKHSIISKVFRNRDGNIVSSEVISDLLTSTENTNNSFGKKETTTNKNTISNSTLPIT

> Spy0872-2 / Schmitz 1/177 (serotype 22); SEQ ID NO: 128
AIINHANDIVKTVTERKIGTATNSSTISKTENIDKESPVGNLVTTAQLTIAKKTFPTVDFAMTNNGGIRSDLV
VKNDRTITWGAAQAVQPFGNILQVIQMTGQHIYDVLNQQYDENQTYFLQMSGLTYTYTDNDPKNSDTPFKIVK
VYKDNGEEINLTTTYTVVVNDFLYGGGDGFSAFKKAKLIGAINTDTEAFITYITNLEASGKTVNATIKGVKNY
VTSNLESSTKVNSAGKHSIISKVFRNRDGNIVSSEIISDLLTSTENTNNSLGKKETTTNKNTISSSTLPIT

> Spy0872-2 / Schmitz 1/234 (serotype 44); SEQ ID NO: 129
AIINHANDIVKTVTERKIGTATNSSTISKTENIDKESPVGNLVTTAQLTIAKKTFPTVDFAMTNNGGIRSDLV
VKNDRTITWGAAQAVQPFGNILQVIQMTGQHIYDVLNQQYDENQTYFLQMSGLTYTYTDNDPKNSDTPFKIVK
VYKDNGEEINLTTTYTVVVNDFLYGGGDGFSAFKKTKLIGAINTDTEAFITYITNLEASGKTVNATIKGVKNY
VTSNLESSTKVNSAGKHSIISKVFRNRDGNIVSSEIISDLLTSTENTNNSLGKKETTTNKNTISSSTLPIT

> Spy0872-2 / Schmitz 1/22 (serotype 4); SEQ ID NO: 130
AIINHANDIVKTVTERKIGTATNSSTISKTENIDKESPVGNLVTTAQLTIAKKTFPTVDFAMTNNGGIRSDLV
VKNDRTITWEAAQAVQPFGNILQVIQMTGQHIYDVLNQQYDENQTYFLQMSGLTYTYTDNDPKNSDTPFKIVK
VYKDNGEEINLTTTYTVVVNDFLYGGGDGFSAFKKAKLIGAINTDTEAFITYITNLEASGKTVNATIKGVKNY
VTSNLESSTKVNSAGKHSIIIISKVFRNRDGNIVSSEIISDLLTSTENTNNSFGKKEITTNKNTISNSTLPIT

5. Further Sequences

> Spy0488 / SF370 (serotype 1); SEQ ID NO: 8
LRQIQSIRLIDVLELAFGVGYKEETTSQFSSDQPSQVVLYRGEANTVRFAYTNQMSLMKDIRIALDGSDKSLT
AQIVPGMGHVYEGFQTSARGIFTMSGVPESTVPVANPNVQTKYIRYFKVIDDMHNTMYKGTVFLVQPQAWKYT
MKSVDQLPVDDLNHIGVAGIERMTTLIKNAGALLTTGGSGAFPDNIKVSINPKGRQATITYGDGSTDIIPPAV
LWKKGSVKEPTEADQSVGTPTPGIPGKFKRDQSLNEHEAMVNVEPLSHVVKDNIKVIDEKSTGRFEPFRPNED
EKEKPASDVKVRPAEVGSWLEPATALPSVEMSAEDRLKS

> Spy0895 / SF370 (serotype 1); SEQ ID NO: 9
TNNQTLDILLDVYAYNHAFRIAKALPNIPKTALYLLEMLKERRELNLAFLAEHAAENRTIEDQYHCSLWLNQS
LEDEQIANYILDLEVKVKNGAIIDFVRSVSPILYRLFLRLITSEIPNFKAYIFDTKNDQYDTWHFQAMLESDH
EVFKAYLSQKQSRNVTTKSLADMLTLTSLPQEIKDLVFLLRHFEKAVRNPLAHLIKPFDEEELHRTTHFSSQA
FLENIITLATFSGVIYRREPFYFDDMNAIIKKELSLWRQSIV

> Spy1536 / SF370 (serotype 1); SEQ ID NO: 131
IEMPGGAYDIRTVLQVNGKEDKRKGAYQFVAVGISRASLAQLLYAWLTPFTEISTAEDTTGGYSDADFLRINQ
FYMETSQNAAIYQALSLAGKPVTLDYKGVYVLDVNNESTFKGTLHLADTVTGVNGKQFTSSAELIDYVSHLKL
GDEVTVQFTSDNKPKKGVGRIIKLKNGKNGIGIALTDHTSVNSEDTVIFSTKGVGGPSAGLMFTLDIYDQITK
EDLRKGRTIAGTGTIGKDGEVGDIGGAGLKVVAAAEAGADIFFVPNNPVDKEIKKVNPNAISNYEEAKRAAKR
LKTKMKIVPVTTVQEALVYLRK

> Spy1666 / SF370 (serotype 1); SEQ ID NO: 132
TKEFHHVTVLLHETVDMLDIKPDGIYVDATLGGSGHSAYLLSKLGEEGHLYCFDQDQKAIDNAQVTLKSYIDK
GQVTFIKDNFRHLKARLTALGVDEIDGILYDLGVSSPQLDERERGFSYKQDAPLDMRMDRQSLLTAYEVVNTY
PFNDLVKIFFKYGEDKFSKQIARKIEQARAIKPIETTTELAELIKAAKPAKELKKKGHPAKQIFQAIRIEVND
ELGAADESIQDAMELLALDGRISVITFHSLEDRLTKQLFKEASTVDVPKGLPLIPEDMKPKFELVSRKPILPS
HSELTANKRAHSAKLRVAKKIRK

> Spy1727 / SF370 (serotype 1); SEQ ID NO: 10
VTTTEQELTLTPLRGKSGKAYKGTYPNGECVFIKLNTTPILPALAKEQIAPQLLWAKRMGNGDMMSAQEWLNG
RTLTKEDMNSKQIIHILLRLHKSKKLVNQLLQLNYKIENPYDLLVDFEQNAPLQIQQNSYLQAIVKELKRSLP
EFKSEVATIVHGDIKHSNWVITTSGMIFLVDWDSVRLTDRMYDVAYLLSHYIPRSRWSEWLSYYGYKNNDKVM
QKIIWYGQFSHLTQILKCFDKRDMEHVNQEIYALRKFREIFRKK

SEQUENCE DATA FOR DNA SEQUENCES

1. Spy0269

1.1 Full length Spy0269

> Spy0269 / SF370 (serotype 1); SEQ ID NO: 133
ATGGACTTAGAACAAACGAAGCCAAACCAAGTTAAGCAGAAAATTGCTTTAACCTCAACAATTGCTTTATTGA
GTGCCAGTGTAGGCGTATCTCACCAAGTCAAAGCAGATGATAGAGCCTCAGGAGAAACGAAGGCGAGTAATAC
TCACGACGATAGTTTACCAAAACCAGAAACAATTCAAGAGGCAAAGGCAACTATTGATGCAGTTGAAAAAACT
CTCAGTCAACAAAAAGCAGAACTGACAGAGCTTGCTACCGCTCTGACAAAAACTACTGCTGAAATCAACCACT
TAAAAGAGCAGCAAGATAATGAACAAAAAGCTTTAACCTCTGCACAAGAAATTTACACTAATACTCTTGCAAG
TAGTGAGGAGACGCTATTAGCCCAAGGAGCCGAACATCAAAGAGAGTTAACAGCTACTGAAACAGAGCTTCAT
AATGCTCAAGCAGATCAACATTCAAAAGAGACTGCATTGTCAGAACAAAAAGCTAGCATTTCAGCAGAAACTA
CTCGAGCTCAAGATTTAGTGGAACAAGTCAAAACGTCTGAACAAAATATTGCTAAGCTCAATGCTATGATTAG
CAATCCTGATGCTATCACTAAAGCAGCTCAAACGGCTAATGATAATACAAAAGCATTAAGCTCAGAATTGGAG
AAGGCTAAAGCTGACTTAGAAAATCAAAAAGCTAAAGTTAAAAAGCAATTGACTGAAGAGTTGGCAGCTCAGA
AAGCTGCTCTAGCAGAAAAAGAGGCAGAACTTAGTCGTCTTAAATCCTCAGCTCCGTCTACTCAAGATAGCAT
TGTGGGTAATAATACCATGAAAGCACCGCAAGGCTATCCTCTTGAAGAACTTAAAAAATTAGAAGCTAGTGGT
TATATTGGATCAGCTAGTTACAATAATTATTACAAAGAGCATGCAGATCAAATTATTGCCAAAGCTAGTCCAG
GTAATCAATTAAATCAATACCAAGATATTCCAGCAGATCGTAATCGCTTTGTTGATCCCGATAATTTGACACC
AGAAGTGCAAAATGAGCTAGCGCAGTTTGCAGCTCACATGATTAATAGTGTAAGAAGACAATTAGGTCTACCA
CCAGTTACTGTTACAGCAGGATCACAAGAATTTGCAAGATTACTTAGTACCAGCTATAAGAAAACTCATGGTA
ATACAAGACCATCATTTGTCTACGGACAGCCAGGGGTATCAGGGCATTATGGTGTTGGGCCTCATGATAAAAC
TATTATTGAAGACTCTGCCGGAGCGTCAGGGCTCATTCGAAATGATGATAACATGTACGAGAATATCGGTGCT
TTTAACGATGTGCATACTGTGAATGGTATTAAACGTGGTATTTATGACAGTATCAAGTATATGCTCTTTACAG
ATCATTTACACGGAAATACATACGGCCATGCTATTAACTTTTTACGTGTAGATAAACATAACCCTAATGCGCC
TGTTTACCTTGGATTTTCAACCAGCAATGTAGGATCTTTGAATGAACACTTTGTAATGTTTCCAGAGTCTAAC
ATTGCTAACCATCAACGCTTTAATAAGACCCCTATAAAAGCCGTTGGAAGTACAAAAGATTATGCCCAAAGAG
TAGGCACTGTATCTGATACTATTGCAGCGATCAAAGGAAAAGTAAGCTCATTAGAAAATCGTTTGTCGGCTAT
TCATCAAGAAGCTGATATTATGGCAGCCCAAGCTAAAGTAAGTCAACTTCAAGGTAAATTAGCAAGCACACTT
AAGCAGTCAGACAGCTTAAATCTCCAAGTGAGACAATTAAATGATACTAAAGGTTCTTTGAGAACAGAATTAC
TAGCAGCTAAAGCAAAACAAGCACAACTCGAAGCTACTCGTGATCAATCATTAGCTAAGCTAGCATCGTTGAA
AGCCGCACTGCACCAGACAGAAGCCTTAGCAGAGCAAGCCGCAGCCAGAGTGACAGCACTGGTGGCTAAAAAA
GCTCATTTGCAATATCTAAGGGACTTTAAATTGAATCCTAACCGCCTTCAAGTGATACGTGAGCGCATTGATA
ATACTAAGCAAGATTTGGCTAAAACTACCTCATCTTTGTTAAATGCACAAGAAGCTTTAGCAGCCTTACAAGC
TAAACAAAGCAGTCTAGAAGCTACTATTGCTACCACAGAACACCAGTTGACTTTGCTTAAAACCTTAGCTAAC
GAAAAGGAATATCGCCACTTAGACGAAGATATAGCTACTGTGCCTGATTTGCAAGTAGCTCCACCTCTTACGG
GCGTAAAACCGCTATCATATAGTAAGATAGATACTACTCCGCTTGTTCAAGAAATGGTTAAAGAAACGAAACA
ACTATTAGAAGCTTCAGCAAGATTAGCTGCTGAAAATACAAGTCTTGTAGCAGAAGCGCTTGTTGGCCAAACC
TCTGAAATGGTAGCAAGTAATGCCATTGTGTCTAAAATCACATCTTCGATTACTCAGCCCTCATCTAAGACAT
CTTATGGCTCAGGATCTTCTACAACGAGCAATCTCATTTCTGATGTTGATGAAAGTACTCAAAGAGCTCTTAA
AGCAGGAGTCGTCATGTTGGCAGCTGTCGGCCTCACAGGATTTAGGTTCCGTAAGGAATCTAAGTGA

1.2 Antigenic fragment Spy0269-1

> Spy0269-1 / SF370 (serotype 1); SEQ ID NO: 11
GATGATAGAGCCTCAGGAGAAACGAAGGCGAGTAATACTCACGACGATAGTTTACCAAAACCAGAAACAATTC
AAGAGGCAAAGGCAACTATTGATGCAGTTGAAAAAACTCTCAGTCAACAAAAAGCAGAACTGACAGAGCTTGC
TACCGCTCTGACAAAAACTACTGCTGAAATCAACCACTTAAAAGAGCAGCAAGATAATGAACAAAAAGCTTTA
ACCTCTGCACAAGAAATTTACACTAATACTCTTGCAAGTAGTGAGGAGACGCTATTAGCCCAAGGAGCCGAAC
ATCAAAGAGAGTTAACAGCTACTGAAACAGAGCTTCATAATGCTCAAGCAGATCAACATTCAAAAGAGACTGC
ATTGTCAGAACAAAAAGCTAGCATTTCAGCAGAAACTACTCGAGCTCAAGATTTAGTGGAACAAGTCAAAACG

TCTGAACAAAATATTGCTAAGCTCAATGCTATGATTAGCAATCCTGATGCTATCACTAAAGCAGCTCAAACGG
CTAATGATAATACAAAAGCATTAAGCTCAGAATTGGAGAAGGCTAAAGCTGACTTAGAAAATCAAAAAGCTAA
AGTTAAAAAGCAATTGACTGAAGAGTTGGCAGCTCAGAAAGCTGCTCTAGCAGAAAAAGAGGCAGAACTTAGT
CGTCTTAAATCCTCAGCTCCGTCTACTCAAGATAGCATTGTGGGTAATAATACCATGAAAGCACCGCAAGGCT
ATCCTCTTGAAGAACTTAAAAAATTAGAAGCTAGTGGTTATATTGGATCAGCTAGTTACAATAATTATTACAA
AGAGCATGCAGATCAAATTATTGCCAAAGCTAGTCCAGGTAATCAATTAAATCAATACCAAGATATTCCAGCA
GATCGTAATCGCTTTGTTGATCCCGATAATTTGACACCAGAAGTGCAAAATGAGCTAGCGCAGTTTGCAGCTC
ACATGATTAATAGTGTAAGAAGACAATTAGGTCTACCACCAGTTACTGTTACAGCAGGATCACAAGAATTTGC
AAGATTACTTAGTACCAGCTATAAGAAAACTCATGGTAATACAAGACCATCATTTGTCTACGGACAGCCAGGG
GTATCAGGGCATTATGGTGTTGGGCCTCATGATAAAACTATTATTGAAGACTCTGCCGGAGCGTCAGGGCTCA
TTCGAAATGATGATAACATGTACGAGAATATCGGTGCTTTTAACGATGTGCATACTGTGAATGGTATTAAACG
TGGTATTTATGACAGTATCAAGTATATGCTCTTTACAGATCATTTACACGGAAATACATACGGCCATGCTATT
AACTTTTTACGTGTAGATAAACATAACCCTAATGCGCCTGTT

1.3 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0269-1 / Schmitz 2/14 (serotype 1); SEQ ID NO: 134
GATGATAGAGCCTCAGGAGAAACGAAGGCGAGTAATACTCACGACGATAGTTTACCAAAACCAGAAACAATTC
AAGAGGCAAAGGCAACTATTGATGCAGTTGAAAAAACTCTCAGTCAACAAAAAGCAGAACTGACAGAGCTTGC
TACCGCTCTGACAAAAACTACTGCTGAAATCAACAACTTAAAAGAGCAGCAAGATAATGAACAAAAAGCTTTA
ACCTCTGCACAAGAAATTTACACTAATACTCTTGCAAGTAGTGAGGAGACGCTATTAGCCCAAGGAGCCGAAC
ATCAAAGAGAGTTAACAGCTACTGAAACAGAGCTTCATAATGCTCAAGCAGATCAACATTCAAAAGAGACTGC
ATTGTCAGAACAAAAAGCTAGCATTTCAGCAGAAACTACTCGAGCTCAAGATTTAGTGGAACAAGTCAAAACG
TCTGAACAAAATATTGCTAAGCTCAATGCTATGATTAGCAATCCTGATGCTATCACTAAAGCAGCTCAAACGG
CTAATGATAATACAAAAGCATTAAGCTCAGAATTGGAGAAGGCTAAAGCTGACTTAGAAAATCAAAAAGCTAA
AGTTAAAAAGCAATTGACTGAAGAGTTGGCAGCTCAGAAAGCTGCTCTAGCAGAAAAAGAGGCAGAACTTAGT
CGTCTTAAATCCTCAGCTCCGTCTACTCAAGATAGCATTGTGGGTAATAATACCATGAAAGCACCGCAAGGCT
ATCCTCTTGAAGAACTTAAAAAATTAGAAGCTAGTGGTTATATTGGATCAGCTAGTTACAATAATTATTACAA
AGAGCATGCAGATCAAATTATTGCCAAAGCTAGTCCAGGTAATCAATTAAATCAATACCAAGATATTCCAGCA
GATCGTAATCGCTTTGTTGATCCCGATAATTTGACACCAGAAGTGCAAAATGAGCTAGCGCAGTTTGCAGCTC
ACATGATTAATAGTGTAAGAAGACAATTAGGTCTACCACCAGTTACTGTTACAGCAGGATCACAAGAATTTGC
AAGATTACTTAGTACCAGCTATAAGAAAACTCATGGTAATACAAGACCATCATTTGTCTACGGACAGCCAGGG
GTATCAGGGCATTATGGTGTTGGGCCTCATGATAAAACTATTATTGAAGACTCTGCCGGAGCGTCAGGGCTCA
TTCGAAATGATGATAACATGTACGAGAATATCGGTGCTTTTAACGATGTGCATACTGTGAATGGTATTAAACG
TGGTATTTATGACAGTATCAAGTATATGCTCTTTACAGATCATTTACACGGAAATACATACGGCCATGCTATT
AACTTTTTACGTGTAGATAAACGTAACCCTAATGCGCCTGTT

> Spy0269-1 / Schmitz 1/156 (serotype 4); SEQ ID NO: 135
GATGATAGAGCCTCAGGAGAAACGAAGGCGAGTAATACTCACGACGATAGTTTACCAAAACCAGAAACAATTC
AAGAGGCAAAGGCAACTATTGATGCAGTTGAAAAAACTCTCAGTCAACAAAAAGCAGAACTGACAGAGCTTGC
TACCGCTCTGACAAAAACTACTGCTGAAATCAACCACTTAAAAGAGCAGCAAGATAATGAACAAAAAGCTTTA
ACCTCTGCACAAGAAATTTACACTAATACTCTTGCAAGTAGTGAGGAGACGCTATTAGCCCAAGGAGCCGAAC
ATCAAAGAGAGTTAACAGCTACTGAAACAGAGCTTCATAATGCTCAAGCAGATCAACATTCAAAAGAGACTGC
ATTGTCAGAACAAAAAGCTAGCATTTCAGCAGAAACTACTCGAGCTCAAGATTTAGTGGAACAAGTCAAAACG
TCTGAACAAAATATTGCTAAGCTCAATGCTATGATTAGCAATCCTGATGCTATCACTAAAGCAGCTCAAACGG
CTAATGATAATACAAAAGCATTAAGCTCAGAATTGGAGAAGGCTAAAGCTGACTTAGAAAATCAAAAAGCTAA
AGTTAAAAAGCAATTGACTGAAGAGTTGGCAGCTCAGAAAGCTGCTCTAGCAGAAAAAGAGGCAGAACTTAGT
CGTCTTAAATCCTCAGCTCCGTCTACTCAAGATAGCATTGTGGGTAATAATACCATGAAAGCACCGCAAGGCT
ATCCTCTTGAAGAACTTAAAAAATTAGAAGCTAGTGGTTATATTGGATCAGCTAGTTACAATAATTATTACAA
AGAGCATGCAGATCAAATTATTGCCAAAGCTAGTCCAGGTAATCAATTAAATCAATACCAAGATATTCCAGCA
GATCGTAATCGCTTTGTTGATCCCGATAATTTGACACCAGAAGTGCAAAATGAGCTAGCGCAGTTTGCAGCTC
ACATGATTAATAGTGTAAGGAGACAATTAGGTCTACCACCAGTTACTGTCACAGCAGGATCACAAGAATTTGC
AAGATTACTTAGTACCAGCTATAAGAAAACTCATGGTAATACAAGACCATCATTTGTCTACGGACAGCCAGGG
GTATCAGGGCATTATGGTGTTGGGCCTCATGATAAAACTATTATTGAAGACTCTGCCGGAGCGTCAGGGCTCA
TTCGAAATGATGATAACATGTACGAGAATATCGGTGCTTTTAACGATGTGCATACTGTGAATGGTATTAAACG
TGGTATTTATGACAGTATCAAGTATATGCTCTTTACAGATCATTTACACGGAAATACATATGGTCATGCTATT
AACTTTTTACGTGTAGATAAACATAACCCTAAGGCGCCTGTT

> Spy0269-1 / Schmitz 1/59 (serotype 12); SEQ ID NO: 136
GATGATAGAGCCTCAGGAGAAACGAAGGCGAGTAATACTCACGACGATAGTTTACCAAAACCAGAAACAATTC

AAGAGGCAAAGGCAACTATTGATGCAGTTGAAAAAACTCTCAGTCAACAAAAAGCAGAACTGACAAAGCTTGC
TACCGCTCTGACAAAAACTACTGCTGAAATCAACCACTTAAAAGAGCAGCAAGATAATGAACAAAAAGCTTTA
ACCTCTGCACAAGAAATTTACACTAATACTCTTGCAAGTAGTGAGGAGACGCTATTAGCCCAAGGAGCCGAAC
ATCAAAGAGAGTTAACAGCTACTGAAACAGAGCTTCATAATGCTCAAGCAGATCAACATTCAAAAGAGACTGC
ATTGTCAGAACAAAAAGCTAGCATTTCAGCAGAAACTACTCGAGCTCAAGATTTAGTGGAACAAGTCAAAACG
TCTGAACAAAATATTGCTAAGCTCAATGCTATGATTAGCAATCCTGATGCTATCACTAAAGCAGCTCAAACGG
CTAATGATAATACAAAAGCATTAAGCTCAGAATTGGAGAAGGCTAAAGCTGACTTAGAAAATCAAAAAGCTAA
AGTTAAAAAGCAATTGACTGAAGAGTTGGCAGCTCAGAAAGCTGCTCTAGCAGAAAAAGAGGCAGAACTTAGT
CGTCTTAAATCCTCAGCTCCGTCTACTCAAGATAGCATTGTGGGTAATAATACCATGAAAGCACCGCAAGGCT
ATCCTCTTGAAGAACTTAAAAAATTAGAAGCTAGTGGTTATATTGGATCAGCTAGTTACAATAATTATTACAA
AGAGCATGCAGATCAAATTATTGCCAAAGCTAGTCCAGGTAATCAATTAAATCAATACCAAGATATTCCAGCA
GATCGTAATCGCTTTGTTGATCCCGATAATTTGACACCAGAAGTGCAAAATGAGCTAGCGCAGTTTGCAGCTC
ACATGATTAATAGTGTAAGAAGACAATTAGGTCTACCACCAGTTACTGTTACAGCAGGATCACAAGAATTTGC
AAGATTACTTAGTACCAGCTATAAGAAAACTCATGGTAATACAAGACCATCATTTGTCTACGGACAGCCAGGG
GTATCAGGGCATTATGGTGTTGGGCCTCATGATAAAACTATTATTGAAGACTCTGCCGGAGCGTCAGGGCTCA
TTCGAAATGATGATAACATGTACGAGAATATCGGTGCTTTTAACGATGTGCATACTGTGAATGGTATTAAACG
TGGTATTTATGACAGTATCAAGTATATGCTCTTTACAGATCATTTACACGGAAATACATACGGCCATGCTATT
AACTTTTTACGTGTAGATAAACGTAACCCTAATGCGCCTGTT

> Spy0269-1 / Schmitz 1/177 (serotype 22); SEQ ID NO: 137
GATGATAGAGCCTCAGGAGAAACGAAGGCGAGTAATACTCACGACGATAGTTTACCAAAACCAGAAACAATTC
AAGAGGCAAAGGCAACTATTGAAGCAGTTGAAAAAGCTCTCAGTCAACAAAAAGCAGAACTGACAGAGCTTGC
TACCGCTCTGACAAAAACTACTGCTAAAATCAACCACTTAAAAGAGCAGCAAGATAATGAACAAAAAGCTTTA
ACCTCTGCACAAGAAATTTACACTAATACTCTTGCAAGTAGTGAGGAGACGCTATTAGCCCAAGGAGCCGAAC
ATCAAAGAGAGTTAACAGCTACTGAAACAGAGCTTCATAATGCTCAAGCAGATCAACATTCAAAAGAGACTGC
ATTGTCAGAACAAAAAGCTAGCATTTCAGCAGAAACTACTCGAGCTCAAGATTTAGTGGAACAAGTCAAAACG
TCTGAACAAAATATTGCTAAGCTCAATGCTATGATTAGTAATCCTGATGCTATCACTAAAGCAGCTCAAACGG
CTAATGATAATACAAAAGCATTAAGCTCAGAATTGGAGAAGGCTAAAGCTGACTTAGAAAATCAAAAAGCTAA
AGTTAAAAAGCAATTGACTGAAGAGTTGGCAGCTCAGAAAGCTGCTCTAGCAGAAAAAGAGGCAGAACTTAGT
CGTCTTAAATCCTCAGCTCCGTCTACTCAAGATAGCATTGTGGGTAATAATACCATGAAAGCACCGCAAGGCT
ATCCTCTTGAAGAACTTAAAAAATTAGAAGCTAGTGGTTATATTGGATCAGCTAGTTACAATAATTATTACAA
AGAGCATGCAGATCAAATTATTGCCAAAGCTAGTCCAGGTAATCAATTAAATCAATACCAAGATATTCCAGCA
GATCGTAATCGCTTTGTTGATCCCGATAATTTGACACCAGAAGTGCAAAATGAGCTAGCGCAGTTTGCAGCTC
ACATGATTAATAGTGTAAGAAGACAATTAGGTCTACCACCAGTTACTGTCACAGCAGGATCACAAGAATTTGC
AAGATTACTTAGTACCAGCTATAAGAAAACTCATGGTAATACAAGACCATCATTTGTCTACGGACAGCCAGGG
GTATCAGGGCATTATGGTGTTGGGCCTCATGATAAAACTATTATTGAAGACTCTGCCGGAGCGTCAGGGCTCA
TTCGAAATGATGATAACATGTACGAGAATATCGGTGCTTTTAACGATGTGCATACTGTGAATGGTATTAAACG
TGGTATTTATGACAGTATCAAGTATATGCTCTTTACAGATCATTTACACGGAAATACATATGGCCATGCTATT
AACTTTTTACGTGTAGATAAACGTAACCCTAATGCGCCTGTT

> Spy0269-1 / Schmitz 1/43 (serotype 22); SEQ ID NO: 138
GATGATAGAGCCTCAGGAGAAACGAAGGCGAGTAATACTCACGACGATAGTTTACCAAAACCAGAAACAATTC
AAGAGGCAAAGGCAACTATTGAAGCAGTTGAAAAAGCTCTCAGTCAACAAAAAGCAGAACTGACAGAGCTTGC
TACCGCTCTGACAAAAACTACTGCTAAAATCAACCACTTAAAAGAGCAGCAAGATAATGAACAAAAAGCTTTA
ACCTCTGCACAAGAAATTTACACTAATACTCTTGCAAGTAGTGAGGAGACGCTATTAGCCCAAGGAGCCGAAC
ATCAAAGAGAGTTAACAGCTACTGAAACAGAGCTTCATAATGCTCAAGCAGATCAACATTCAAAAGAGACTGC
ATTGTCAGAACAAAAAGCTAGCATTTCAGCAGAAACTACTCGAGCTCAAGATTTAGTGGAACAAGTCAAAACG
TCTGAACAAAATATTGCTAAGCTCAATGCTATGATTAGTAATCCTGATGCTATCACTAAAGCAGCTCAAACGG
CTAATGATAATACAAAAGCATTAAGCTCAGAATTGGAGAAGGCTAAAGCTGACTTAGAAAATCAAAAAGCTAA
AGTTAAAAAGCAATTGACTGAAGAGTTGGCAGCTCAGAAAGCTGCTCTAGCAGAAAAAGAGGCAGAACTTAGT
CGTCTTAAATCCTCAGCTCCGTCTACTCAAGATAGCATTGTGGGTAATAATACCATGAAAGCACCGCAAGGCT
ATCCTCTTGAAGAACTTAAAAAATTAGAAGCTAGTGGTTATATTGGATCAGCTAGTTACAATAATTATTACAA
AGAGCATGCAGATCAAATTATTGCCAAAGCTAGTCCAGGTAATCAATTAAATCAATACCAAGATATTCCAGCA
GATCGTAATCGCTTTGTTGATCCCGATAATTTGACACCAGAAGTGCAAAATGAGCTAGCGCAGTTTGCAGCTC
ACATGATTAATAGTGTAAGAAGACAATTAGGTCTACCACCAGTTACTGTCACAGCAGGATCACAAGAATTTGC
AAGATTACTTAGTACCAGCTATAAGAAAACTCATGGTAATACAAGACCATCATTTGTCTACGGACAGCCAGGG
GTATCAGGGCATTATGGTGTTGGGCCTCATGATAAAACTATTATTGAAGACTCTGCCGGAGCGTCAGGGCTCA
TTCGAAATGATGATAACATGTACGAGAATATCGGTGCTTTTAACGATGTGCATACTGTGAATGGTATTAAACG
TGGTATTTATGACAGTATCAAGTATATGCTCTTTACAGATCATTTACACGGAAATACATATGGCCATGCTATT
AACTTTTTACGTGTAGATAAACGTAACCCTAATGCGCCTGTT

> Spy0269-1 / Schmitz 1/136 (serotype 25); SEQ ID NO: 139

GATGATAGAGCCTCAGGAGAAACGAAGGCGAGTAATACTCACGACGATAGTTTACCAAAACCAGAAACAATTC
AAGAGGCAAAGGCAACTATTGATGCAGTTGAAAAAACTCTCAGTCAACAAAAAGCAGAACTGACAGAGCTTGC
TACCGCTCTGACAAAAACTACTGCTGAAATCAACCACTTAAAAGAGCAGCAAGATAATGAACAAAAAGCTTTA
ACCTCTGCACAAGAAATTTACACTAATACTCTTGCAAGTAGTGAGGAGACGCTATTAGCCCAAGGAGCCGAAC
ATCAAAGAGAGTTAACAGCTACTGAAACAGAGCTTCATAATGCTCAAGCAGATCAACATTCAAAAGAGACTGC
ATTGTCAGAACAAAAAGCTAGCATTTCAGCAGAAACTACTCGAGCTCAAGATTTAGTGGAACAAGTCAAAACG
TCTGAACAAAATATTGCTAAGCTCAATGCTATGATTAGCAATCCTGATGCTATCACTAAAGCAGCTCAAACGG
CTAATGATAATACAAAAGCATTAAGCTCAGAATTGGAGAAGGCTAAAGCTGACTTAGAAAATCAAAAAGCTAA
AGTTAAAAAGCAATTGACTGAAGAGTTGGCAGCTCAGAAAGCTGCTCTAGCAGAAAAAGAGGCAGAACTTAGT
CGTCTTAAATCCTCAGCTCCGTCTACTCAAGATAGCATTGTGGGTAATAATACCATGAAAGCACCGCAAGGCT
ATCCTCTTGAAGAACTTAAAAAATTAGAAGCTAGTGGTTATATTGGATCAGCTAGTTACAATAATTATTACAA
AGAGCATGCAGATCAAATTATTGCCAAAGCTAGTCCAGGTAATCAATTAAATCAATACCAAGATATTCCAGCA
GATCGTAATCGCTTTGTTGATCCCGATAATTTGACACCAGAAGTGCAAAATGAGCTAGCGCAGTTTGCAGCTC
ACATGATTAATAGTGTAAGAAGACAATTAGGTCTACCACCAGTTACTGTTACAGCAGGATCACAAGAATTTGC
AAGATTACTTAGTACCAGCTATAAGAAAACTCATGGTAATACAAGACCATCATTTGTCTACGGACAGCCAGGG
GTATCAGGGCATTATGGTGTTGGGCCTCATGATAAAACTATTATTGAAGACTCTGCCGGAGCGTCAGGGCTCA
TTCGAAATGATGATAACATGTACGAGAATATCGGTGCTTTTAACGATGTGCATACTGTGAATGGTATTAAACG
TGGTATTTATGACAGTATCAAGTATATGCTCTTTACAGATCATTTACACGGAAATACATACGGCCATGCTATT
AACTTTTTACGTGTAGATAAACGTAACCCTAATGCGCCTGTT

> Spy0269-1 / Schmitz 1/85 (serotype 28); SEQ ID NO: 140

GATGATAGAGCCTCAGGAGAAACGAAGGCGAGTAATACTCACGACGATAGTTTACCAAAACCAGAAACAATTC
AAGAGGCAAAGGCAACTATTGATGCAGTTGAAAAAACTCTCAGTCAACAAAAAGCAGAACTGACAGAGCTTGC
TACCGCTCTGACAAAAACTACTGCTGAAATCAACCACTTAAAAGAGCAGCAAGATAATGAACAAAAAGCTTTA
ACCTCTGCACAAGAAATTTACACTAATACTCTTGCAAGTAGTGAGGAGACGCTATTAGCCCAAGGAGCCGAAC
ATCAAAGAGAGTTAACAGCTACTGAAACAGAGCTTCATAATGCTCAAGCAGATCAACATTCAAAAGAGACTGC
ATTGTCAGAACAAAAAGCTAGCATTTCAGCAGAAACTACTCGAGCTCAAGATTTAGTGGAACAAGTCAAAACG
TCTGAACAAAATATTGCTAAGCTCAATGCTATGATTAGCAATCCTGATGCTATCACTAAAGCAGCTCAAACGG
CTAATGATAATACAAAAGCATTAAGCTCAGAATTGGAGAAGGCTAAAGCTGACTTAGAAAATCAAAAAGCTAA
AGTTAAAAAGCAATTGACTGAAGAGTTGGCAGCTCAGAAAGCTGCTCTAGCAGAAAAAGAGGCAGAACTTAGT
CGTCTTAAATCCTCAGCTCCGTCTACTCAAGATAGCATTGTGGGTAATAATACCATGAAAGCACCGCAAGGCT
ATCCTCTTGAAGAACTTAAAAAATTAGAAGCTAGTGGTTATATTGGATCAGCTAGTTACAATAATTATTACAA
AGAGCATGCAGATCAAATTATTGCCAAAGCTAGTCCAGGTAATCAATTaAATCAATACCAAGatattccagca
gatcgtaatcgctttGTTGATCCCGATAATTTGACACCAGAAGTGCAAAATGAGCTAGCGCAGTTTGCAGCTC
ACATGATTAATAGTGTAAGAAGACAATTAGGTCTACCACCAGTTACTGTTACAGCAGGATCACaagaatttgc
aagattacttagtaccagctataagaaaactcatggtaatacaagaccatcatttgtctACGGACAGCCAGGG
GTATCAGGGCATTATGGTGTTGGGCCTCATGATAAAACTATTATTGAAGACTCTGCCGGAGCGTCAGGGCTCA
TTCGAAATGATGATAACATGTACGAGAATATCGGTGCTTTTAACGATGTGCATACTGTGAATGGTATTAAACG
TGGTATTTATGACAGTATCAAGTATATGCTCTTTACAGATCATTTACACGGAAATACATACGGCCATGCTATT
AACTTTTTACGTGTAGATAAACATAACCCTAATGCGCCTGTT

> Spy0269-1 / Schmitz 2/50 (serotype 28); SEQ ID NO: 141

GATGATAGAGCCTCAGGAGAAACGAAGGCGAGTAATACTCACGACGATAGTTTACCAAAACCAGAAACAATTC
AAGAGGCAAAGGCAACTATTGATGCAGTTGAAAAAACTCTCAGTCAACAAAAAGCAGAACTGACAGAGCTTGC
TACCGCTCTGACAAAAACTACTGCTGAAATCAACCACTTAAAAGAGCAGCAAGATAATGAACAAAAAGCTTTA
ACCTCTGCACAAGAAATTTACACTAATACTCTTGCAAGTAGTGAGGAGACGCTATTAGCCCAAGGAGCCGAAC
ATCAAAGAGAGTTAACAGCTACTGAAACAGAGCTTCATAATGCTCAAGTAGATCAACATTCAAAAGAGACTGC
ATTGTCAGAACAAAAAGCTAGCATTTCAGCAGAAACTACTCGAGCTCAAGATTTAGTGGAACAAGTCAAAACG
TCTGAACAAAATATTGCTAAGCTCAATGCTATGATTAGCAATCCTGATGCTATCACTAAAGCAGCTCAAACGG
CTAATGATAATACAAAAGCATTAAGCTCAGAATTGGAGAAGGCTAAAGCTGACTTAGAAAATCAAAAAGCTAA
AGTTAAAAAGCAATTGACTGAAGAGTTGGCAGCTCAGAAAGCTGCTCTAGCAGAAAAAGAGGCAGAACTTAGT
CGTCTTAAATCCTCAGCTCCGTCTACTCAAGATAGCATTGTGGGTAATAATACCATGAAAGCACCGCAAGGCT
ATCCTCTTGAAGAACTTAAAAAATTAGAAGCTAGTGGTTATATTGGATCAGCTAGTTACAATAATTATTACAA
AGAGCATGCAGATCAAATTATTGCCAAAGCTAGTCCAGGTAATCAATTAAATCAATACCAAGATATtCCAGCA
GATCGTAATCGCTTTGTTGATCCCGATAATTTGACACCAGAAGTGCAAaATGAGCTAGCGCAGTTTGCAGCTC
ACATGATTAATAGTGTAAGAAGACAATTAGGTCTACCACCAGTTACTGTTACAGCAGGATCACAAGAATTTGC
AAGATTACTTAGTACCAGCTATAAGAAGACTCATGGTAATACAAGACCATCATTTGTCTACGGACAGCCAGGG
GTATCAGGGCATTATGGTGTTGGGCCTCATGATAAAACTATTATTGAAGACTCTGCCGGAGCGTCAGGGCTCA

TTCGAAATGATGATAACATGTACGAGAATATCGGTGCTTTTAACGATGTGCATACTGTGAATGGTATTAAACG
TGGTATTTATGACAGTATCAAGTATATGCTCTTTACAGATCATTTACACGGAAATACATACGGCCATGCTATT
AACTTTTTACGTGTAGATAAACGTAACCCTAATGCGCCTGTT

> Spy0269-1 / Schmitz 1/123 (serotype 49); SEQ ID NO: 142
GATGATAGAGCCTCAGGAGAAACGAAGGCGAGTAATACTCACGACGATAGTTTACCAAAACCAGAAACAATTC
AAGAGGCAAAGGCAACTATTGATGCAGTTGAAAAAACTCTCAGTCAACAAAAAGCAGAACTGACAGAGCTTGC
TACCGCTCTGACAAAAACTACTGCTGAAATCAACCACTTAAAAGAGCAGCAAGATAATGAACAAAAAGCTTTA
ACCTCTGCACAAGAAATTTACACTAATACTCTTGCAAGTAGTGAGGAGACGCTATTAGCCCAAGGAGCCGAAC
ATCAAAGAGAGTTAACAGCTACTGAAACAGAGCTTCATAATGCTCAAGCAGATCAACATTCAAAAGAGACTGC
ATTGTCAGAACAAAAAGCTAGCATTTCAGCAGAAACTACTCGAGCTCAAGATTTAGTGGAACAAGTCAAAACG
TCTGAACAAAATATTGCTAAGCTCAATGCTATGATTAGCAATCCTGATGCTATCACTAAAGCAGCTCAAACGG
CTAATGATAATACAAAAGCATTAAGCTCAGAATTGGAGAAGGCTAAAGCTGACTTAGAAAATCAAAAAGCTAA
AGTTAAAAAGCAATTGACTGAAGAGTTGGCAGCTCAGAAAGCTGCTCTAGCAGAAAAAGAGGCAGAACTTAGT
CGTCTTAAATCCTCAGCTCCGTCTACTCAAGATAGCATTGTGGGTAATAATACCATGAAAGCACCGCAAGGCT
ATCCTCTTGAAGAACTTAAAAAATTAGAAGCTAGTGGTTATATTGGATCAGCTAGTTACAATAATTATTACAA
AGAGCATGCAGATCAAATTATTGCCAAAGCTAGTCCAGGTAATCAATTAAATCAATACCAAGATATtCCAGCA
GAtcgtaatcgctttGTTGATCCCGATAATTTGACACCAGAAGTGCAAAATGAGCTAGCGCAGTTTGCAGCTC
ACATGATTAATAGTGTAAGGAGACAATTAGGTCTACCACCAGTTACTGTTACAGCAGGATCACAAGAATTTGC
AAGATTACTTAGTACCAGCTATAAGAAAACTCATGGTAATACAAGACCATCATTTGTCTACGGACAACCAGGG
GTATCAGGGCATTATGGTGTTGGGCCTCATGATAAAACTATTATTGAAGACTCTGCCGGAGCGTCAGGGCTCA
TTCGAAATGATGATAACATGTACGAGAATATCGGTGCTTTTAACGATGTGCATACTGTGAATGGTATTAAACG
TGGTATTTATGACAGTATCAAGTATATGCTCTTTACAGATCATTTACACGGAAATACATATGGCCATGCTATT
AACTTTTTACGTGTAGATAAACGTAACCCTAATGCGCCTGTT

> Spy0269-1 / Schmitz 1/176 (serotype 83); SEQ ID NO: 143
GATGATAGAGCCTCAGGAGAAACGAAGGCGAGTAATACTCACGACGATAGTTTACCAAAACCAGAAACAATTC
AAGAGGCAAAGGCAACTATTGAAGCAGTTGAAAAAACTCTCAGTCAACAAAAAGCAGAACTGACAGAGCTTGC
TACCGCTCTGACAAAAACTACTGCTGAAATCAACCACTTAAAAGAGCAGCAAGATAACGAACAAAAAGCTTTA
ACCTCTGCACAAGAAATTTACACTAATACTCTTGCAAGTAGTGAGGAGACGCTATTAGCCCAAGGAGCCGAAC
ATCAAAGAGAGTTAACAGCTACTGAAACAGAGCTTCATAATGCTCAAGCAGATCAACATTCAAAAGAGACTGC
ATTGTCAGAACAAAAAGCTAGCATTTCAGCAGAAACTACTCGAGCTCAAGATTTAGTGGAACAAGTCAAAACG
TCTGAACAAAATATTGCTAAGCTCAATGCTATGATTAGCAATCCTGATGCTATCACTAAAGCAGCTCAAACGG
CTAATGATAATACAAAAGCATTAAGCTCAGAATTGGAGAAGGCTAAAGCTGACTTAGAAAATCAAAAAGCTAA
AGTTAAAAAGCAATTGACTGAAGAGTTGGCAGCTCAGAAAGCTGCTCTAGCAGAAAAAGAGGCAGAACTTAGT
CGTCTTAAATCCTCAGCTCCGTCTACTCAAGATAGCATTGTGGGTAATAATACCATGAAAGCACCGCAAGGCT
ATCCTCTTGAAGAACTTAAAAAATTAGAAGCTAGTGGTTATATTGGATCAGCTAGTTACAATAATTATTACAA
AGAGCATGCAGATCAAATTATTGCCAAAGCTAGTCCAGGTAATCAATtAAATCAATACCAAGatATTCCAGCA
Gatcgtaatcgctttgttgatcccgataatttgacaccagaagtgcaaaatgagctagcgcagtttgcagctc
ACATGATTAATAGTGTAAGAAGACAATTAGGTCTACCACCAGTTACTGTCACAGCAGGATCACAAGAATTTGC
AAGATTACTTAGTACCAGCTATAAGAAAACTCATGGTAATACAAGACCATCATTTGTCTACGGACAGCCAGGG
GTATCAGGGCATTATGGTGTTGGGCCTCATGATAAAACTATTATTGAAGACTCTGCCGGAGCGTCAGGGCTCA
TTCGAAATGATGATAACATGTACGAGAATATCGGTGCTTTTAACGATGTGCATACTGTGAATGGTATTAAACG
TGGTATTTATGACAGTATCAAGTATATGCTCTTTACAGATCATTTACACGGAAATACATATGGCCATGCTATT
AACTTTTTACGTGTAGATAAACGTAACCCTAATGCGCCTGTT

2. Spy0292

2.1 Full length Spy0292

> Spy0292 / SF370 (serotype 1); SEQ ID NO: 144
ATGATCAAACGATTAATTTCCCTAGTGGTCATCGCCTTATTTTTTGCAGCAAGCACTGTTAGCGGTGAAGAGT
ATTCGGTAACTGCTAAGCATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAGATGCTAA
AGAAGTTGTCCCAGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTCTAAGGGC
AAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTCACTACAAACTATACTATTAGTA
ACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACGCCAATAG
CCCCGCTATTGCTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAAACAATTA
AGACAATGGGGCATTTCCGATGCAAAGGTCGTCAATTCAACTGGCTTAACTAACCATTTTTTAGGAGCTAATA
CTTATCCTAATACAGAACCAGATGATGAAAATTGTTTTTGCGCCACTGATTTAGCTATTATTGCCAGGCATCT
CTTATTAGAATTTCCAGAAGTACTGAAATTATCTAGCAAATCCTCCACTATTTTTGCTGGACAAACCATTTAC

AGTTATAATTACATGCTTAAAGGCATGCCTTGTTATCGAGAAGGCGTGGATGGTCTTTTTGTTGGTTATTCTA
AAAAAGCCGGTGCTTCTTTTGTAGCTACTAGTGTCGAAAATCAAATGAGGGTTATTACAGTAGTTTTAAATGC
TGATCAAAGCCACGAGGATGATTTAGCTATATTTAAAACAACCAATCAATTGTTGCAGTACCTTTTAATTAAT
TTTCAAAAAGTCCAGTTAATTGAAAATAATAAACCAGTAAAAACGTTATATGTCTTAGACAGTCCTGAAAAAA
CTGTCAAACTTGTAGCCCAAAATAGTTTATTTTTTATCAAACCAATACATACAAAGACCAAAAATACCGTCCA
TATTACTAAGAAATCATCCACAATGATCGCACCTCTATCAAAGGGACAAGTCTTAGGTAGAGCAACCCTTCAA
GATAAACATCTTATTGGACAAGGTTATCTGGATACTCCTCCTTCTATCAATCTTATCCTTCAAAAAAACATTT
CTAAAAGTTTCTTTTTAAAGGTCTGGTGGAACCGTTTTGTGAGGTATGTCAATACCTCTTTATAG

2.2 Antigenic fragment Spy0292-1

> Spy0292-1 / SF370 (serotype 1); SEQ ID NO: 12
GAAGAGTATTCGGTAACTGCTAAGCATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG
ATGCTAAAGAAGTTGTCCCAGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTCACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGCTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA
ACAATTAAGACAATGGGGCATTTCCGATGCAAAGGTCGTCAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAACCAGATGATGAAAATTGTTTTTGC

2.3 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0292-1 / Schmitz 1/39 (serotype 12); SEQ ID NO: 145
GAAGAGTATTCGGTAACTGCTAAGCATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG
ATGCTAAAGAAGTTGTCCCAGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTCACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGCTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA
ACAATTAAGACAATGGGGCATTTCCGATGCAAAGGTCGTCAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAACCagaTGATGAAAATTGTTTTTGC

> Spy0292-1 / Schmitz 1/55 (serotype 118); SEQ ID NO: 146
GAAGAGTATTCGGTAACTGCTAAGCATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG
ATGCTAAAGAAGTTGTCCCAGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTTACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGCTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA
ACAATTAAGACAATGGGGCATTTCCGATACAAAGGTCGTCAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAACCAGATGATGAAAATTGTTTTTGC

> Spy0292-1 / Schmitz 1/56 (serotype 28); SEQ ID NO: 147
GAAGAGTATTCGGTAACTGCTAAGCATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG
ATACTAAAGAAGTTGTCCCAGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTCACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGCTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA
ACAATTAAGGCAATGGGGCATTTCCGATGCAAAGGTCGTTAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAACCAGATGATGAAAATTGTTTTTGC

> Spy0292-1 / Schmitz 1/74 (serotype 3); SEQ ID NO: 148
GAAGAGTATTCGGTAACTGCTAAACATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG
ATGCTAAAGAGGTTGTCCCAGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTCACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGcTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA
ACAATTAAGACAATGGGGCATTTCCGATGCAAAGGTCGTCAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAACCAGATGATGAAAATTGTTTTTGC

> Spy0292-1 / Schmitz 1/76 (serotype 22); SEQ ID NO: 149
GAAGAGTATTCGGTAACTGCTAAGCATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG

ATGCTAAAGAAGTTGTCCCTGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTCACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGCTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA
ACAATTAAGACAATGGGGCATTTCCGATGCAAAGGTCGTCAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAAccagATGATGAAAATTGTTTTTGC

> Spy0292-1 / Schmitz 1/92 (serotype 11); SEQ ID NO: 150
GAAGAGTATTCGGTAACTGCTAAGCATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG
ATGCTAAAGAAGTTGTCCCAGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTCACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGCTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA
ACAATTAAGGCAATGGGGCATTTCCGATGCAAAGGTCGTTAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAACCAGATGATGaaaATTGTTTTTGC

> Spy0292-1 / Schmitz 1/94 (serotype 1); SEQ ID NO: 151
GAAGAGTATTCGGTAACTGCTAAGCATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG
ATGCTAAAGAAGTTGTCCCAGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTCACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGCTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA
ACAATTAAGACAATGGGGCATTTCCGATGCAAAGGTCGTCAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAACCAGATGATGAAAATTGTTTTTGC

> Spy0292-1 / Schmitz 1/142 (serotype 83); SEQ ID NO: 152
GAAGAGTATTCGGTAACTGCTAAGCATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG
ATGCTAAAGAGGTTGTCCCAGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTCACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGCTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA
ACAATTAAGACAATGGGGCATTTCCGATGCAAAGGTCGTCAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAAccagaTGATGAAAATTGTTTTTGC

> Spy0292-1 / Schmitz 1/144 (serotype 76); SEQ ID NO: 153
GAAGAGTATTCGGTAACTGCTAAGCATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG
ATGCTAAAGAAGTTGTCCCTGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTCACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGCTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA
ACAATTAAGACAATGGGGCATTTCCGATGCAAAGGTCGTCAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAaccagaTGATGAAAATTGTTTTTGC

> Spy0292-1 / Schmitz 1/194 (serotype 44); SEQ ID NO: 154
GAAGAGTATTCGGTAACTGCTAAGCATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG
ATGCTAAAGAAGTTGTCCCTGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTCACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGCTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA
ACAATTAAGACAATGGGGCATTTCCGATGCAAAGGTCGTCAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAACCAGATGATGAAAATTGTTTTTGC

2.4 Antigenic fragment Spy0292-3

> Spy0292-3 / SF370 (serotype 1); SEQ ID NO: 13
GAAGAGTATTCGGTAACTGCTAAGCATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG
ATGCTAAAGAAGTTGTCCCAGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTCACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGCTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA

ACAATTAAGACAATGGGGCATTTCCGATGCAAAGGTCGTCAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAACCAGATGATGAAAATTGTTTTTGCGCCACTGATTTAGCTATTATTGCCA
GGCATCTCTTATTAGAATTTCCAGAAGTACTGAAATTATCTAGCAAATCCTCCACTATTTTTGCTGGACAAAC
CATTTACAGTTATAATTACATGCTTAAAGGCATGCCTTGTTATCGAGAAGGCGTGGATGGTCTTTTTGTTGGT
TATTCTAAAAAAGCCGGTGCTTCTTTTGTAGCTACTAGTGTCGAAAATCAAATGAGGGTTATTACAGTAGTTT
TAAATGCTGATCAAAGCCACGAGGATGATTTAGCTATATTTAAAACAACCAATCAATTGTTGCAGTACCTTTT
AATTAATTTTCAAAAAGTCCAGTTAATTGAA

2.5 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0292-3 / Schmitz 1/39 (serotype 12); SEQ ID NO: 155
GAAGAGTATTCGGTAACTGCTAAGCATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG
ATGCTAAAGAAGTTGTCCCAGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTCACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGCTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA
ACAATTAAGACAATGGGGCATTTCCGATGCAAAGGTCGTCAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAACcagaTGATGAAAATTGTTTTTGCGCCACTGATTTAGCTATTATTGCCA
GGCATCTCTTATTAGAATTTCCAGAAGTACTGAAATTATCTAGCAAATCCTCCACTATTTTTGATGGACAAAC
CATTTACAGTTATAATTACATGCTTAAAGGCATGCCTTGTTATCGAGAAGGCGTGGATGGTCTTTTTGTTGGT
TATTCTAAAAAAGCCGGTGCTTCTTTTGTAGCTACTAGTGTCGAAAATCAAATGAGGGTTATTACAGTAGTTT
TAAATGCTGATCAAAGCCACGAGGATGATTTAGCTATATTTAAAACAACCAATCAATTGTTGCAGTACCTTTT
AATTAATTTTCAAAAAGTCCAGTTAATTGAA

> Spy0292-3 / Schmitz 1/55 (serotype 118); SEQ ID NO: 156
GAAGAGTATTCGGTAACTGCTAAGCATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG
ATGCTAAAGAAGTTGTCCCAGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTTACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGCTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA
ACAATTAAGACAATGGGGCATTTCCGATACAAAGGTCGTCAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAACCAGATGATGAAAATTGTTTTTGCGCCACTGATTTAGCTATTATTGCCA
GGCATCTCTTATTAGAATTTCCAGAAGTACTGAAATTATCTAGCAAATCCTCCACTATTTTTGATGGACAAAC
CATTTACAGTTATAATTACATGCTTAAAGGCATGCCTTGTTATCGAGAAGGCGTGGATGGTCTCTTTGTCGGT
TATTCTAAAAAAGCCGGTGCTTCTTTTGTAGCTACTAGTGTCGAAAATCAAATGAGGGTTATTACAGTAGTTT
TAAATGCTGATCAAAGCCACGAGGATGATTTAGCTATATTTAAAACAACCAATCAATTGTTGCAGTACCTTTT
AATTAATTTTCAAAAAGTCCAGTTAATTGAA

> Spy0292-3 / Schmitz 1/56 (serotype 28); SEQ ID NO: 157
GAAGAGTATTCGGTAACTGCTAAGCATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG
ATACTAAAGAAGTTGTCCCAGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTCACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGCTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA
ACAATTAAGGCAATGGGGCATTTCCGATGCAAAGGTCGTTAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAACCAGATGATGAAAATTGTTTTTGCGCCACTGATTTAGCTATTATTGCCA
GGCATCTCTTATTAGAATTTCCAGAAGTACTGAAATTATCTAGCAAATCCTCCACTATTTTTGATGGACAAAC
CATTTACAGTTATAATTACATGCTTAAAGGCATGCCTTGTTATCGAGAAGGCGTGGATGGTCTTTTTGTTGGT
TATTCTAAAAAAGCCGGTGCTTCTTTTGTAGCTACTAGTGTCGAAAATCAAATGAGGGTTATTACAGTAGTTT
TAAATGCTGATCAAAGCCACGAGGATGATTTAGCTATATTTAAAACAACCAATCAATTGTTGCAGTACCTTTT
AATTAATTTTCAAAAAGTCCAGTTAATTGAA

> Spy0292-3 / Schmitz 1/74 (serotype 3); SEQ ID NO: 158
GAAGAGTATTCGGTAACTGCTAAACATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG
ATGCTAAAGAGGTTGTCCCAGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTCACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGcTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA
ACAATTAAGACAATGGGGCATTTCCGATGCAAAGGTCGTCAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAACCAGATGATGAAAATTGTTTTTGCGCCACTGATTTAGCTATTATTGCCA

GGCATCTCTTATTAGAATTTCCAGAAGTACTGAAATTATCTAGCAAATCCTCCACTATTTTTGCTGGACAAAC
CATTTACAGTTATAATTACATGCTTAAAGGCATGCCTTGTTATCGAGAAGGCGTGGATGGTCTTTTTGTTGGT
TATTCTAAAAAAGCCGGTGCTTCTTTTGTAGCTACTAGTGTCGAAAATCAAATGAGGGTTATTACAGTAGTTT
TAAATGCTGATCAAAGCCACGAGGATGATTTAGCTATATTTAAAACAACCAATCAATTGTTGCAGTACCTTTT
AATTAATTTTCAAAAAGTCCAGTTAATTGAA

> Spy0292-3 / Schmitz 1/76 (serotype 22); SEQ ID NO: 159
GAAGAGTATTCGGTAACTGCTAAGCATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG
ATGCTAAAGAAGTTGTCCCTGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTCACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGCTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA
ACAATTAAGACAATGGGGCATTTCCGATGCAAAGGTCGTCAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAAccagATGATGAAAATTGTTTTTGCGCCACTGATTTAGCTATTATTGCCA
GGCATCTCTTATTAGAATTTCCAGAAGTACTGAAATTATCTAGCAAATCCTCCACTATTTTTGATGGACAAAC
CATTTACAGTTATAATTACATGCTTAAAGGCATGCCTTGTTATCGAGAAGGCGTGGATGGTCTTTTTGTTGGT
TATTCTAAAAAAGCCGGTGCTTCTTTTGTAGCTACTAGTGTCGAAAATCAAATGAGGGTTATTACAGTAGTTT
TAAATGCTGATCAAAGCCACGAGGATGATTTAGCTATATTTAAAACAACCAATCAATTGTTGCAGTACCTTTT
AATTAATTTTCAAAAAGTCCAGTTAATTGAA

> Spy0292-3 / Schmitz 1/92 (serotype 11); SEQ ID NO: 160
GAAGAGTATTCGGTAACTGCTAAGCATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG
ATGCTAAAGAAGTTGTCCCAGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTCACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGCTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA
ACAATTAAGGCAATGGGGCATTTCCGATGCAAAGGTCGTTAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAACCAGATGATGaaaATTGTTTTTGCGCCACTGATTTAGCTATTATTGCCA
GGCATCTCTTATTAGAATTTCCAGAAGTACTGAAATTATCTAGCAAATCCTCCACTATTTTTGATGGACAAAC
CATTTACAGTTATAATTACATGCTTAAAGGCATGCCTTGTTATCGAGAAGGCGTGGATGGTCTTTTTATTGGT
TATTCTAAAAAAGCCGGTGCTTCTTTTGTAGCTACTAGTGTCGAAAATCAAATGAGGGTTATTACAGTAGTTT
TAAATGCTGATCAAAGCCACGAGGATGATTTAGCTATATTTAAAACAACCAATCAATTGTTGCAGTACCTTTT
AATTAATTTTCAAAAAGTCCAGTTAATTGAA

> Spy0292-3 / Schmitz 1/94 (serotype 1); SEQ ID NO: 161
GAAGAGTATTCGGTAACTGCTAAGCATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG
ATGCTAAAGAAGTTGTCCCAGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTCACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGCTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA
ACAATTAAGACAATGGGGCATTTCCGATGCAAAGGTCGTCAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAACCAGATGATGAAAATTGTTTTTGCGCCACTGATTTAGCTATTATTGCCA
GGCATCTCTTATTAGAATTTCCAGAAGTACTGAAATTATCTAGCAAATCCTCCACTATTTTTGCTGGACAAAC
CATTTACAGTTATAATTACATGCTTAAAGGCATGCCTTGTTATCGAGAAGGCGTGGATGGTCTTTTTGTTGGT
TATTCTAAAAAAGCCGGTGCTTCTTTTGTAGCTACTAGTGTCGAAAATCAAATGAGGGTTATTACAGTAGTTT
TAAATGCTGATCAAAGCCACGAGGATGATTTAGCTATATTTAAAACAACCAATCAATTGTTGCAGTACCTTTT
AATTAATTTTCAAAAAGTCCAGTTAATTGAA

> Spy0292-3 / Schmitz 1/142 (serotype 83); SEQ ID NO: 162
GAAGAGTATTCGGTAACTGCTAAGCATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG
ATGCTAAAGAGGTTGTCCCAGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTCACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGCTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA
ACAATTAAGACAATGGGGCATTTCCGATGCAAAGGTCGTCAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAAccagaTGATGAAAATTGTTTTTGCGCCACTGATTTAGCTATTATTGCCA
GGCATCTCTTATTAGAATTTCCAGAAGTACTGAAATTATCTAGCAAATCCTCCACTATTTTTGATGGACAAAC
CATTTACAGTTATAATTACATGCTTAAAGGCATGCCTTGTTATCGAGAAGGCGTGGATGGTCTTTTTGTTGGT
TATTCTAAAAAAGCCGGTGCTTCTTTTGTAGCTACTAGTGTCGAAAATCAAATGAGGGTTATTACAGTAGTTT
TAAATGCTGATCAAAGCCACGAGGATGATTTAGCTATATTTAAAACAACCAATCAATTGTTGCAGTACCTTTT

AATTAATTTTCAAAAAGTCCAGTTAATTGAA

> Spy0292-3 / Schmitz 1/144 (serotype 76); SEQ ID NO: 163
GAAGAGTATTCGGTAACTGCTAAGCATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG
ATGCTAAAGAAGTTGTCCCTGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTCACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGCTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA
ACAATTAAGACAATGGGGCATTTCCGATGCAAAGGTCGTCAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAaccagaTGATGAAAATTGTTTTTGCGCCACTGATTTAGCTATTATTGCCA
GGCATCTCTTATTAGAATTTCCAGAAGTACTGAAATTATCTAGCAAATCCTCCACTATTTTTGATGGACAAAC
CATTTACAGTTATAATTACATGCTTAAAGGCATGCCTTGTTATCGAGAAGGCGTGGATGGTCTTTTTGTTGGT
TATTCTAAAAAAGCCGGTGCTTCTTTTGTAGCTACTAGTGTCGAAAATCAAATGAGGGTTATTACAGTAGTTA
TAAATGCTGATCAAAGCCACGAGGATGATTTAGCTATATTTAAAACAACCAATCAATTGTTGCAGTACCTTTT
AATTAATTTTCAAAAAGTCCAGTTAATTGAA

> Spy0292-3 / Schmitz 1/194 (serotype 44); SEQ ID NO: 164
GAAGAGTATTCGGTAACTGCTAAGCATGCGATTGCCGTTGACCTTGAAAGTGGCAAAGTTTTATACGAAAAAG
ATGCTAAAGAAGTTGTCCCTGTCGCCTCAGTCAGTAAGCTCTTGACAACCTATCTGGTTTACAAAGAAGTTTC
TAAGGGCAAGCTAAATTGGGATAGTCCTGTAACTATTTCTAACTACCCTTATGAACTCACTACAAACTATACT
ATTAGTAACGTTCCTCTTGATAAGAGAAAATATACCGTTAAAGAACTTTTAAGTGCGTTAGTTGTTAATAACG
CCAATAGCCCCGCTATTGCTTTAGCTGAAAAAATAGGCGGAACCGAACCCAAATTTGTTGACAAAATGAAAAA
ACAATTAAGACAATGGGGCATTTCCGATGCAAAGGTCGTCAATTCAACTGGCTTAACTAACCATTTTTTAGGA
GCTAATACTTATCCTAATACAGAACCAGATGATGAAAATTGTTTTTGCGCCACTGATTTAGCTATTATTGCCA
GGCATCTCTTATTAGAATTTCCAGAAGTACTGAAATTATCTAGCAAATCCTCCACTATTTTTGCTGGACAAAC
CATTTACAGTTATAATTACATGCTTAAAGGCATGCCTTGTTATCGAGAAGGCGTGGATGGTCTTTTTGTTGGT
TATTCTAAAAAAGCCGGTGCTTCTTTTGTAGCTACTAGTGTCGAAAATCAAATGAGGGTTATTACAGTAGTTT
TAAATGCTGATCAAAGCCACGAGGATGATTTAGCTATATTTAAAACAACCAATCAATTGTTGCAGTACCTTTT
AATTAATTTTCAAAAAGTCCAGTTAATTGAA

3. Spy0416A

3.1 Full length Spy0416A

> Spy0416A / SF370 (serotype 1); SEQ ID NO: 165
GCAGATGAGCTAAGCACAATGAGCGAACCAACAATCACGAATCACGCTCAACAACAAGCGCAACATCTCACCA
ATACAGAGTTGAGCTCAGCTGAATCAAAATCTCAAGACACATCACAAATCACTCTCAAGACAAATCGTGAAAA
AGAGCAATCACAAGATCTAGTCTCTGAGCCAACCACAACTGAGCTAGCTGACACAGATGCAGCATCAATGGCT
AATACAGGTTCTGATGCGACTCAAAAAAGCGCTTCTTTACCGCCAGTCAATACAGATGTTCACGATTGGGTAA
AAACCAAAGGAGCTTGGGACAAGGGATACAAAGGACAAGGCAAGGTTGTCGCAGTTATTGACACAGGGATCGA
TCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAAAATCAAAAGAAGACATGCTAGCA
CGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGTTGTTTTTGCACATAATTATGTGG
AAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTTGATGAGGACTGGGAAAACTTTGAGTTTGATGC
AGAGGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATCGTCCCCAATCAACCCAGGCACCGAAAGAAACT
GTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACAAACAGACGATGACACCAAATACG
AGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAAGAAGCCGCTGCTACTGGAGAACGCTT
TTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTGCCAACGACATCATGGGATCAGCTGAA
TCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGGAGCAGATGTGATCAACCTGAGTCTTGGAACCG
CTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAAAAAGCTAAAAAAGCCGGTGTATC
AGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATGATCCATTGGCGACAAATCCAGAC
TATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTGGCAGCTATAAACAGTAAGTGGGTGA
TTCAACGTCTAATGACGGTCAAAGAATTAGAAAACCGTGCCGATTTAAACCATGGTAAAGCCATCTATTCAGA
GTCTGTCGACTTTAAAGACATAAAAGATAGCCTAGGTTATGATAAATCGCATCAATTTGCTTATGTCAAAGAG
TCAACTGATGCGGGTTATAACGCACAAGACGTTAAAGGTAAAATTGCTTTAATTGAACGTGATCCCAATAAAA
CCTATGACGAAATGATTGCTTTGGCTAAGAAACATGGAGCTCTGGGAGTACTTATTTTTAATAACAAGCCTGG
TCAATCAAACCGCTCAATGCGTCTAACAGCTAATGGGATGGGGATACCATCTGCTTTCATATCGCACGAATTT
GGTAAGGCCATGTCCCAATTAAATGGCAATGGTACAGGAAGTTTAGAGTTTGACAGTGTGGTCTCAAAAGCAC
CGAGTCAAAAAGGCAATGAAATGAATCATTTTTCAAATTGGGGCCTAACTTCTGATGGCTATTTAAAACCTGA
CATTACTGCACCAGGTGGCGATATCTATTCTACCTATAACGATAACCACTATGGTAGCCAAACAGGAACAAGT
ATGGCCTCTCCTCAGATTGCTGGCGCCAGCCTTTTGGTCAAACAATACCTAGAAAAGACTCAGCCAAACTTGC

CAAAAGAAAAAATTGCTGATATCGTTAAGAACCTATTGATGAGCAATGCTCAAATTCATGTTAATCCAGAGAC
AAAAACGACCACCTCACCGCGTCAGCAAGGGGCAGGATTACTTAATATTGACGGAGCTGTCACTAGCGGCCTT
TATGTGACAGGAAAAGACAACTATGGCAGTATATCATTAGGCAACATCACAGATACGATGACGTTTGATGTGA
CTGTTCACAACCTAAGCAATAAAGACAAAACATTACGTTATGACACAGAATTGCTAACAGATCATGTAGACCC
ACAAAAGGGCCGCTTCACTTTGACTTCTCACTCCTTAAAAACGTACCAAGGAGGAGAAGTTACAGTCCCAGCC
AATGGAAAAGTGACTGTAAGGGTTACCATGGATGTCTCACAGTTCACAAAAGAGCTAACAAAACAGATGCCAA
ATGGTTACTATCTAGAAGGTTTTGTCCGCTTTAGAGATAGTCAAGATGACCAACTAAATAGAGTAAACATTCC
TTTTGTTGGTTTTAAAGGGCAATTTGAAAACTTAGCAGTTGCAGAAGAGTCCATTTACAGATTAAAATCTCAA
GGCAAAACTGGTTTTTACTTTGATGAATCAGGTCCAAAAGACGATATCTATGTCGGTAAACACTTTACAGGAC
TTGTCACTCTTGGTTCAGAG

3.2 Antigenic fragment Spy0416A-1

> Spy0416A-1 / SF370 (serotype 1); SEQ ID NO: 14
GCAGATGAGCTAAGCACAATGAGCGAACCAACAATCACGAATCACGCTCAACAACAAGCGCAACATCTCACCA
ATACAGAGTTGAGCTCAGCTGAATCAAAATCTCAAGACACATCACAAATCACTCTCAAGACAAATCGTGAAAA
AGAGCAATCACAAGATCTAGTCTCTGAGCCAACCACAACTGAGCTAGCTGACACAGATGCAGCATCAATGGCT
AATACAGGTTCTGATGCGACTCAAAAAAGCGCTTCTTTACCGCCAGTCAATACAGATGTTCACGATTGGGTAA
AAACCAAAGGAGCTTGGGACAAGGGATACAAAGGACAAGGCAAGGTTGTCGCAGTTATTGACACAGGGATCGA
TCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAAAATCAAAAGAAGACATGCTAGCA
CGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGTTGTTTTTGCACATAATTATGTGG
AAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTTGATGAGGACTGGGAAAACTTTGAGTTTGATGC
AGAGGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATCGTCCCCAATCAACCCAGGCACCGAAAGAAACT
GTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACAAACAGACGATGACACCAAATACG
AGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAAGAAGCCGCTGCTACTGGAGAACGCTT
TTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTGCCAACGACATCATGGGATCAGCTGAA
TCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGGAGCAGATGTGATCAACCTGAGTCTTGGAACCG
CTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAAAAAGCTAAAAAAGCCGGTGTATC
AGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATGATCCATTGGCGACAAATCCAGAC
TATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTGGCAGCTATAAACAGTAAGTGGGTGA
TTCAACGTCTAATGACGGTCAAAGAATTAGAAAACCGTGCCGATTTAAACCATGGTAAAGCCATCTATTCAGA
GTCTGTCGACTTTAAAGACATAAAAGATAGCCTAGGTTATGATAAATCGCATCAATTTGCTTATGTCAAAGAG
TCAACTGATGCGGGTTATAACGCACAAGACGTTAAAGGTAAAATTGCTTTAATTGAACGTGATCCCAATAAAA
CCTATGACGAAATGATTGCTTTGGCTAAGAAACATGGAGCTCTGGGAGTACTTATTTTTAATAACAAGCCTGG
TCAATCAAACCGCTCAATGCGTCTAACAGCTAATGGGATGGGGATACCATCTGCTTTCATATCGCACGAATTT
GGTAAGGCCATGTCCCAATTAAATGGCAATGGTACAGGAAGTTTAGAGTTTGACAGTGTGGTCTCAAAAGCAC
CGAGTCAAAAAGGCAATGAAATGAATCATTTTTCAAATTGGGGCCTAACTTCTGATGGCTATTTAAAACCTGA
CATTACTGCACCAGGTGGCGATATCTATTCTACCTATAACGATAACCACTATGGTAGCCAAACAGGAACAAGT
ATGGCCTCTCCTCAGATTGCTGGCGCCAGCCTTTTGGTCAAACAATACCTAGAAAAGACTCAGCCAAACTTGC
CAAAAGAAAAAATTGCTGATATCGTTAAGAACCTATTGATGAGCAATGCTCAAATTCATGTTAATCCAGAGAC
AAAAACGACCACCTCACCGCGTCAGCAAGGGGCA

3.3 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0416A-1 / Schmitz 1/7 (serotype 4); SEQ ID NO: 166
GCAGATGAGCTAACCACAACGAGTGAACCAACAATCACGAATCACGCTCAACAACAAGCGCAACATCTCACCA
ATACAGAGTTGAGCTCAGCTGAATCACAATCCCCAGACACATCACAAATCACTCCCAAGACAAATCGTGAAAA
AGAGCAACCACAAGGTCTAGTCTCTGAGCCAACCACAACTGAGCTAGCTGACACAGATGCAGCATCAATGGCT
AATACAGGTCCTGATGCGACTCAAAAAAGCGCTTCTTTACCGCCAGTCAATACAGATGTTCACGATTGGGTAA
AAACCAAAGGAGCTTGGGACAAGGGATACAAAGGACAAGGCAAGGTTGTCGCAGTTATTGACACAGGGATCGA
TCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAAAATCAAAAGAAGACATGCTAGCA
CGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGTTGTTTTTGCACATAATTATGTGG
AAAATAGCGATAATATCAAAGAAAATCAATTCGGGGATTTTGATGAGGACTGGGAAAACTTTGAGTTTGATGC
AGAGCCAAAAGCCATCAAAAAAAACAAGATCTATCGTCCCCAATCAACCCAGGCACCGAAAGAAACTGTTATC
AAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACAAACAGACGATGACACCAAATACGAGTCAC
ACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAAGAAGCCGCTGCTACTGGAGAACGCTTTTTAGG
AATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTGCCAACGACGTCATGGGATCAGCTGAATCACTC
TTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGGAGCAGATGTGATCAACCTGAGTCTTGGAACCGCTAATG
GGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAAAAAGCTAAAAAAGCCGGTGTATCAGTTGT
TGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATGATCCATTGGCAACAAATCCAGACTATGGT

TTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTGGCAGCTATAAACAGTAAGTGGGTGATTCAAC
GTCTAATGACGGCCAAAGAATTAGAAAACCGTGCCGATTTAAACCATGGTAAAGCCATCTATTCAGAGTCTGT
CGActttaaagacataaaagatagcctaggttatgataaATCGCATCAATTTGCTTATGTCAAaGAGTCAACT
GATGCGGGTTATAAAGCACAAGACGTTAAAGATAAAATTGCTTTAATTGAACGTGATCCCAATAAAACCTATG
ACGAAATGATTGCTTTGGCTAAGAAACATGGAGCCCTGGGAGTACTTATTTTTAATAACAAGCCTGGTCAATC
AAACCGCTCAATGCGTCTAACAGCTAATGGGATGGGGATACCATCTGCTTTCATATCGCACGAATTTGGTAAG
GCCATGTCCCAATTAAATGGCAATGGTACAGGAAGTTTAGAGTTTGACAGTGTGGTCTCAAAAGCACCGAGTC
AAAAAGGCAATGAAATGAATCATTTTTCAAATTGGGGCCTAACTTCTGATGGCTATTTAAAACCTGACATTAC
TGCACCAGGTGGCGATATCTACTCTACCTATAACGATAACCACTATGGTAGCCAAACAGGAACAAGTATGGCC
TCTCCTCAGATTGCTGGCGCCAGCCTTTTGGTCAAACAATACCTAGAAAAGACTCAGCCAAACTTGCCAAAAG
AAAAAATTGCTGATATCGTTAAGAACCTATTGATGAGCAATGCTCAAATTCATGTTAATCCAGAGACAAAAAC
GACCACCTCACCGCGTCAGCAAGGGGCA

> Spy0416A-1 / Schmitz 1/39 (serotype 12); SEQ ID NO: 167
GCAGATGAGCTAACCACAACGAGTGAACCAACAATCACGAATCACACTCAACAACAAGCGCAACATCTCACCA
ATACAGAGTTGAGCTCAGCTGAATCAAAACCTCAAGACACATCACAAATCACTCTCAAGACAAATCGTGAAAA
AGAGCAACCACAAGGTCTAGTCTCTGAGCCAACCACAACTGAGCTAGCTGACACAGATGCAGCACCAATGGCT
AATACAGGTCCTGATGCGACTCAAAAAAGCGCTTCTTTACCGCCAGTCAATACAGATGTTCACGATTGGGTAA
AAACCAAAGGAGCTTGGGACAAGGGATACAAAGGACAAGGCAAGGTTGTCGCAGTTATTGACACAGGGATCGA
TCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAAAATCAAAAGAAGACATGCTAGCA
CGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGTTGTTTTTGCACATAATTATGTGG
AAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTTGATGAGGACTGGGAAAACTTTGAGTTTGATGC
AGAGGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATCGTCCCCAATCAACCCAGGCACCGAAAGAAACT
GTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACAAACAGACGATGACACCAAATACG
AGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAAGAAGCCGCTGCTACTGGAGAACGCTT
TTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTGCCAACGACGTCATGGGATCAGCTGAA
TCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGGAGCAGATGTGATCAACCTGAGTCTTGGAACCG
CTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAAAAAGCTAAAAAAGCCGGTGTATC
AGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATGATCCATTGGCAACAAATCCAGAC
TATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTGGCAGCTATAAACAGTAAGTGGGTGA
TTCAACGTCTAATGACGGTCAAAGAATTAGAAAACCGTGCCGATTTAAACCATGGTAAAGCCATCTaTTCAGA

> Spy0416A-1 / Schmitz 1/55 (serotype 118); SEQ ID NO: 168
GCAGATGAGCTAACCACAACGAGTGAACCAACAATCACGAATCACGCTCAACAACAAGCGCCACCTCTCACCA
ATACAGAGTTGAGCTCAGCTGAATCACAACCTCAAGACACATCACAAGTAACTCCAGAGACAAATCGTGAAAA
AGAGCAACCACAAGGTCTAGTCTCTGAGCCAACAACAACTGAGCTAGCTGACACAGATGCAGCACCAATGGCT
AATACAGGTTCTGATGCGACTCAAAAAAGCGCTTCTTTACCGCCAGTCAATACAGATGTTCACGATTGGGTAA
AAACCAAAGGAGCTTGGGACAAGGGATACAAAGGACAAGGCAAGGTTGTCGCAGTTATTGACACAGGGATCGA
TCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAAAATCAAAAGAAGACATGCTAGCA
CGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGTTGTTTTTGCACATAATTATGTGG
AAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTTGATGAGGACTGGGAAAACTTTGAGTTTGATGC
AGAGGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATCGTCCCCAATCAACCCAGGCACCGAAAGAAACT
GTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACAAACAGACGATGACACCAAATACG
AGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAAGAAGCCGCTGCTACTGGAGAACGCTT
TTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTGCCAACGACGTCATGGGATCAGCTGAA
TCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCCTTAGGAGCAGATGTGATCAACCTGAGTCTTGGAACCG
CTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAAAAAGCTAAAAAAGCCGGTGTATC
AGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATGATCCATTGGCGACAAATCCAGAC
TATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTAGCAGCTATAAACAGTAAGTGGGTGA
TTCAACGTCTAATGACGGTCAAAGAATTGGAAAACCGTGCCGATTTAAACCATGGTAAAGCCATCTaTTCAGA

GTCTGTCGACTTTAAAGACATAAAAGATAGCCTAGGTTATGATAAATCGCATCAATTTGCTTATGTCAaAGAG
TCAACTGATGCGGGTTATAACGCACAAAACGTTAAAGGTAAAATTGCTTTAATTGAACGTGATCCCAATAAAA
CCTATGACGAAATGATTGCTTTGGCTAAGAAACATGGAGCCCTGGGAGTACTTATTTTTAATAACAAGCCTGG
TCAATCAAACCGCTCAATGCGTCTAACAGCTAATGGGATGGGGATACCATCTGCTTTCATATCGCACGAATTT
GGTAAGGCCATGTCCCAATTAAATGGCAATGGTACAGGAAGTTTAGAGTTTGACAGTGTGGTCTCAAAAGCAC
CGAGTCAAAAAGGCAATGAAATGAATCATTTTTCAAATTGGGGCCTAACCTCTGATGGCTATTTAAAACCTGA
CATTACTGCACCAGGTGGCGATATCTACTCTACCTATAACGATAACCACTATGGTAGCCAAACAGGAACAAGT
ATGGCCTCTCCTCAGATTGCTGGCGCCAGCCTTTTGGTCAAACAATACCTAGAAAAGACTCAGCCAAATTTGC
CAAAAGAAAAAATTGCTGATATCGTTAAGAACCTATTGATGAGCAATGCTCAAATTCATGTTAATCCAGAGAC
AAAAACGACCACCTCACCGCGTCAGCAAGGGGCA

> Spy0416A-1 / Schmitz 1/56 (serotype 28); SEQ ID NO: 169
GCAGATGAGCTAACCACAACGAGTGAACCAACAATCACGAATCACGCTCAACAACAAGCGCAACATCTCACCA
ATACAGAGTTGAGCTCAGCTGAATCACAATCCCCAGACACATCACAAATCACTCCCAAGATAAATCGTGAAAA
AGAGCAACCACAAGGTCTAGTCTCTGAGCCAACCACAACTGAGCTAGCTGACACAGATGCAGCACCAATGGCT
AATACAGGTCCTGATGCGACTCAAAAAAGCGCTTCTTTACCGCCAGTCAATACAGATGTTCACGATTGGGTAA
AAACCAAAGGAGCTTGGGACAAGGGGTACAAAGGACAAGGTAAGGTTGTCGCAGTTATTGACACAGGGATCGA
TCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAAAATCAAAAGAAGACATGCTAGCA
CGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGTTGTTTTTGCACATAATTATGTGG
AAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTTGATGAGGACTGGGAAAACTTTGAGTTTGATGC
AGAGCCAAAAGCCATCAAAAAACACAAGATCTATCGTCCCCAATCAACCCAGGCACCGAAAGAAACTGTTATC
AAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACAAACAGACGATGACACCAAATACGAGTCAC
ACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGTAAAGAAGCCGCTGCTACTGGAGAACGCTTTTTAGG
AATTGCACCAGAGACCCAAGTCATGTTCATGCGTGTTTTTGCCAACGACGTCATGGGATCAGCTGAATCACTC
TTTATCAAAGCTATCGAAGATGCCGTGGCCTTAGGAGCAGATGTGATCAACCTGAGTCTTGGGACCGCTAATG
GTGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAAAAAGCTAAAAAAGCCGGTGTATCAGTTGT
TGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATGATCCATTGGCAACAAATCCAGACTATGGT
TTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTGGCAGCTATAAACAGTAAGTGGGTGATTCAAC
GTCTAATGACGGTCAAAGAATTAGAAAACCGTGCCGATTTAAACCATGGTAAAGCCATCTaTTCAGAGTCTGT
CGACTTTtAAAGACATAAAAGATAGCCTAGGTTATGATAAATCGCATCAATTTGCTTATGTCAAAGAGTCAACT
GATGCGGGTTATAACGCACAAGACGTTAAAGGTAAAATTGCTTTAATTGAACGTGATCCCAATAAAACCTATG
ACGAAATGATTGCTTTGGCTAAGAAACATGGAGCCCTGGGAGTACTTATTTTTAATAACAAGCCTGGTCAATC
AAACCGCTCAATGCGCCTAACAGCTAATGGGATGGGGATACCATCTGCTTTCATATCGCACGAATTTGGTAAG
GCCATGTCCCAATTAAATGGCAATGGTACAGGAAGTTTAGAGTTTGACAGTGTGGTCTCAAAAGCACCGAGTC
AAAAAGGCAATGAAATGAATCATTTTTCAAATTGGGGCCTAACTTCTGATGGCTATTTAAAACCTGACATTAC
TGCACCAGGGGGTGATATCTACTCTACCTATAACGATAACCACTATGGTAGCCAAACAGGAACAAGTATGGCC
TCTCCTCAGATTGCTGGCGCCAGCCTTTTGGTCAAACAATACCTAGAAAAGACTCAGCCAAACTTGCCAAAAG
AAAAAATTGCTGATATCGTTAAGAACCTATTGATGAGCAATGCTCAAATTCATGTTAATCCAGAGACAAAAAC
GACCACCTCACCGCGTCAGCAAGGGGCA

> Spy0416A-1 / Schmitz 1/94 (serotype 1); SEQ ID NO: 170
GCAGATGAGCTAAGCACAATGAGCGAACCAACAATCACGAATCACGCTCAACAACAAGCGCAACATCTCACCA
ATACAGAGTTGAGCTCAGCTGAATCAAAATCTCAAGACACATCACAAATCACTCTCAAGACAAATCGTGAAAA
AGAGCAATCACAAGATCTAGTCTCTGAGCCAACCACAACTGAGCTAGCTGACACAGATGCAGCATCAATGGCT
AATACAGGTTCTGATGCGACTCAAAAAAGCGCTTCTTTACCGCCAGTCAATACAGATGTTCACGATTGGGTAA
AAACCAAAGGAGCTTGGGACAAGGGATACAAAGGACAAGGCAAGGTTGTCGCAGTTATTGACACAGGGATCGA
TCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAAAATCAAAAGAAGACATGCTAGCA
CGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGTTGTTTTTGCACATAATTATGTGG
AAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTTGATGAGGACTGGGAAAACTTTGAGTTTGATGC
AGAGGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATCGTCCCCAATCAACCCAGGCACCGAAAGAAACT
GTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACAAACAGACGATGACACCAAATACG
AGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAAGAAGCCGCTGCTACTGGAGAACGCTT
TTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTGCCAACGACATCATGGGATCAGCTGAA
TCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGGAGCAGATGTGATCAACCTGAGTCTTGGAACCG
CTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAAAAAGCTAAAAAAGCCGGTGTATC
AGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATGATCCATTGGCGACAAATCCAGAC
TATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTGGCAGCTATAAACAGTAAGTGGGTGA
TTCAACGTCTAATGACGGTCAAAGAATTAGAAAACCGTGCCGATTTAAACCATGGTAAAGCCATCTATTCAGA
GTCTGTCGACTTTAAAGACATAAAAGATAGCCTAGGTTATGATAAATCGCATCAATTTGCTTATGTCaAAGAG
TCAACTGATGCGGGTTATAACGCACAAGACGTTAAAGGTAAAATTGCTTTAATTGAACGTGATCCCAATAAAA

CCTATGACGAAATGATTGCTTTGGCTAAGAAACATGGAGCTCTGGGAGTACTTATTTTTAATAACAAGCCTGG
TCAATCAAACCGCTCAATGCGTCTAACAGCTAATGGGATGGGGATACCATCTGCTTTCATATCGCACGAATTT
GGTAAGGCCATGTCCCAATTAAATGGCAATGGTACAGGAAGTTTAGAGTTTGACAGTGTGGTCTCAAAAGCAC
CGAGTCAAAAAGGCAATGAAATGAATCATTTTTCAAATTGGGGCCTAACTTCTGATGGCTATTTAAAACCTGA
CATTACTGCACCAGGTGGCGATATCTATTCTACCTATAACGATAACCACTATGGTAGCCAAACAGGAACAAGT
ATGGCCTCTCCTCAGATTGCTGGCGCCAGCCTTTTGGTCAAACAATACCTAGAAAAGACTCAGCCAAACTTGC
CAAAAGAAAAAATTGCTGATATCGTTAAGAACCTATTGATGAGCAATGCTCAAATTCATGTTAATCCAGAGAC
AAAAACGACCACCTCACCGCGTCAGCAAGGGGCA

> Spy0416A-1 / Schmitz 1/253 (serotype 49); SEQ ID NO: 171
GCAGATGAGCTAACCACAACGAGTGAACCAACAATCACGAATCACGCTCAACAACAAGCGCAACCTCTCACCA
ATACAGAGTTGAGCTCAGCTGAATCACAATCCCCAGACATATCACAAGTAACTCCAGAGACAAATCGTGAAAA
AGAGCAACCACAAGGTCTAGTCTCTGAGCCAACAACAACTGAGCTAGCTGACACAGATGCAGCACCAATGGCT
AATACAGGTCCTGATGCGACTCAAAAAAGCGCTTCTTTACCGCCAGTCAATACAGATGTTCACGATTGGGTAA
AAACCAAAGGAGCTTGGGACAAGGGATACAAAGGACAAGGCAAGGTTGTCGCAGTTATTGACACAGGGATCGA
TCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAAAATCAAAAGAAGACATGCTAGCA
CGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGTTGTTTTTGCACATAATTATGTGG
AAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTTGATGAGGACTGGGAAAACTTTGAGTTTGATGC
AGATGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATCGTCCCCAATCAACCCAGGCACCGAAAGAAACT
GTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACAAACAGACGATGACACCAAATACG
AGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAAGAAGCCGCTGCTACTGGAGAACGCTT
TTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTGCCAACGACGTCATGGGATCAGCTGAA
TCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGGAGCAGATGTGATCAACCTGAGTCTTGGAACCG
CTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAAAAAGCTAAAAAAGCCGGTGTATC
AGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATGATCCATTGGCAACAAATCCAGAC
TATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTGGCAGCTATAAACAGTAAGTGGGTGA
TTCAACGTCTAATGACGGTCAAAGGATTAGAAAACCGTGCCGATTTAaACCATGGTAAAGCCATCTATTCAGA
GTCTGTCGACTTTAAAGACATAAAAGATAGCCTAGGTTATGATAAATCGCATCAATTTGCTTATGTCAAaGAG
TCAACTGATGCGGGTTATAACGCACAAGACGTTAAAGGTAAAATTGCTTTAATTGAACGTGATCCCAATAAAA
CCTATGACGAAATGATTGCTTTGGCTAAGAAACATGGAGCCCTGGGACTACTTATTTTTAATAACAAGTCTGG
TCAATCAAACCGCTCAATGCGTCTAACAGCTAATGGGATGGGGATACCATCTGCTTTCATATCGCACGAATTT
GGTAAGGCCATGTCCCAATTAAATGGCAATGGTACAGGAAGTTTAGAGTTTGACAGTGTGGTCTCAAAAGCAC
CGAGTCAAAAAGGCAATGAAATGAATCATTTTTCAAATTGGGGCCTAACTTCTGATGGCTATTTAAAACCTGA
CATTACTGCACCAGGTGGCGATATCTACTCTACCTATAACGATAACCACTATGGTAGCCAAACAGGAACAAGT
ATGGCCTCTCCTCAGATTGCTGGCGCCAGCCTTTTGGTCAAACAATACCTAGAAAAGACCCAGCCAAACTTGC
CAAAAGAAAAAATTGCTGATATCGTTAAGAACCTATTGATGAGCAATGCTCAAATTCATGTTAATCCAGAGAC
AAAAACAACCACCTCACCGCGTCAGCAAGGGGCA

> Spy0416A-1 / Schmitz 1/174 (serotype 6); SEQ ID NO: 172
GCAGATGAGCTAACCACAACGAGTGAACCAACAATCACGAATCACGCTCAACAACAAGCGCAACATCTCACCA
ATACAGAGTTGAGCTCAGCTGAATCAAAACCTCAAGACACATCACAAATCACTCCCAAGACAAATCGTGAAAA
AGAGCAATCACAAGATCTAGTCTCTGAGCCAACCACAACTGAGCTAGCTGACACAGATGCAGCATCAATGGCT
AATACAGGTCCTGATGCGACTCAAAAAAGCGCTTCTTTACCGCCAGTCAATACAGATGTTCACGATTGGGTAA
AAACCAAAGGAGCTTGGGACAAGGGATACAAAGGACAAGGCAAGGTTGTCGCAGTTATTGACACAGGGATCGA
TCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAAAATCAAAAGAAGACATGCTAGCA
CGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGTTGTTTTTGCACATAATTATGTGG
AAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTTGATGAGGACTGGGAAAACTTTGAGTTTGATGC
AGAGGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATCGTCCCCAATCAACCCAGGCACCGAAAGAAACT
GTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACAAACAGACGATGACACCAAATACG
AGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAAGAAGCCGCTGCTACTGGAGAACGCTT
TTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTGCCAACGACGTCATGGGATCAGCTGAA
TCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGGAGCAGATGTGATCAACCTGAGTCTTGGAACCG
CTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAAAAAGCTAAAAAAGCCGGTGTATC
AGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATGATCCATTGGCAACAAATCCAGAC
TATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTGGCAGCTATAAACAGTAAGTGGGTGA
TTCAACGTCTAATGACGGTCAAAGAATTAGAAAACCGTGCCGATTTAAACCATGGTAAAGCCATCTaTTCAGA
GTCTGTCGACTTTAAAaACATAAAAGATAGCCTAGGTTATGATAAATCGCATCAATTTGCTTATGTCAAaGAG
TCAACTGATGCGGGTTATAACGCACAAGACGTTAAAGGTAAAATTGCTTTAATTGAACGTGATCCCAATAAAA
CCTATGACGAAATGATTGCTTTGGCTAAGAAACATGGAGCCCTGGGAGTACTTATTTTTAATAACAAACCTGG
TCAATCAAACCGCTCAATGCGCCTAACATCTAATGGGATGGGAATACCATCTGCTTTCATATCGCACGAATTT

GGTAAGGCCATGTCCCAATTAAATGGCAATGGTACAGGAAGTTTAGAGTTTGACAGTGTGGTCTCAAAAGCAC
CGAGTCAAAAAGGCAATGAAATGAATCATTTTTCAAATTGGGGCCTAACTTCTGATGGCTATTTAAAACCTGA
CATTACTGCACCAGGTGGCGATATCTACTCTACCTATAACGATAACCACTATGGTAGCCAAACAGGAACAAGT
ATGGCCTCTCCTCAGATTGCTGGCGCCAGCCTTTTGGTCAAACAATACCTAGAAAAGACTCAGCCAAACTTGC
CAAAAGAAAAAATTGCTGATATCGTTAAGAACCTATTGATGAGCAATGCTCAAATTCATGTTAATCCAGAGAC
AAAAACGACCACCTCACCGCGTCAGCAAGGGGCA

> Spy0416A-1 / Schmitz 1/176 (serotype 83); SEQ ID NO: 173
GCAGATGAGCTAACCACAACGAGTGAACCAACAATCACGAATCACACTCAACAACAAGCGCAACATCTCACCA
ATACAGAGTTGAGCTCAGCTGAATCAAAACCTCAAGACACATCACAAATCACTCTCAAGACAAATCGTGAAAA
AGAGCAACCACAAGGTCTAGTCTCTGAGCCAACCACAACTGAGCTAGCTGACACAGATGCAGCACCAATGGCT
AATACAGGTCCTGATGCGACTCAAAAAAGCGCTTCTTTACCGCCAGTCAATACAGATGTTCACGATTGGGTAA
AAACCAAAGGAGCTTGGGACAAGGGATACAAAGGACAAGGCAAGGTTGTCGCAGTTATTGACACAGGGATCGA
TCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAAAATCAAAAGAAGACATGCTAGCA
CGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGTTGTTTTTGCACATAATTATGTGG
AAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTTGATGAGGACTGGGAAAACTTTGAGTTTGATGC
AGAGGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATCGTCCCCAATCAACCCAGGCACCGAAAGAAACT
GTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACAAACAGACGATGACACCAAATACG
AGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAAGAAGCCGCTGCTACTGGAGAACGCTT
TTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTGCCAACGACGTCATGGGATCAGCTGAA
TCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGGAGCAGATGTGATCAACCTGAGTCTTGGAACCG
CTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAAAAAGCTAAAAAAGCCGGTGTATC
AGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATGATCCATTGGCAACAAATCCAGAC
TATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTGGCAGCTATAAACAGTAAGTGGGTGA
TTCAACGTCTAATGACGGTCAAAGAATTAGAAAACCGTGCCGATTTAAACCATGGTAAAGCCATCTATTCAGA
GTCTGTCGACTTTAAAAACATAAAAGATAGCCTAGGTTATGATAAATCGCATCAATTTGCTTATGTCAAAGAG
TCAACTGATGCGGGTTATAAAGCACAAGACGTTAAAGGTAAAATTGCTTTAATTGAACGTGATCCCAATAAAA
CCTATGACGAAATGATTGCTTTGGCTAAGAAACATGGAGCCCTGGGAGTACTTATTTTTAATAACAAGCCTGG
TCAATCAAACCGCTCAATGCGTCTAACAGCTAATGGGATGGGGATACCATCTGCTTTCATATCGCACGAATTT
GGTAAGGCCATGTCCCAATTAAATGGCAATGGTACAGGAAGTTTAGAGTTTGACAGTGTGGTCTCAAAAGCAC
CGAGTCAAAAAGGCAATGAAATGAATCATTTTTCAAATTGGGGCCTAACTTCTGATGGCTATTTAAAACCTGA

> Spy0416A-1 / Schmitz 1/234 (serotype 44); SEQ ID NO: 174
GCAGATGAGCTAAGCACAATGAGTGAACCAACAATCACGAATCACGCTCAACAACAAGCGCAACATCTCACCA
ATACAGAGTTGAGCTCAGCTGAATCAAAATCTCAAGACACATCACAAATCACTCCCAAGACAAATCGTGAAAA
AGAGCAATCACAAGATCTAGTCTCTGAGCCAACAACAACTGAGCTAGCTGACACAGATGCAGCATCAATGGCT
AATACAGGTTCTGATGCGACTCAAAAAAGCGCTTCTTTACCGCCAGTCAATACAGATGTTCACGATTGGGTAA
AAACCAAAGGAGCTTGGGACAAGGGATACAAAGGACAAGGCAAGGTTGTCGCAGTTATTGACACAGGGATCGA
TCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAAAATCAAAAGAAGACATGCTAGCA
CGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGTTGTTTTTGCACATAATTATGTGG
AAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTTGATGAGGACTGGGAAAACTTTGAGTTTGATGC
AGATGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATCGTCCCCAATCAACCCAGGCACCGAAAGAAACT
GTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACAAACAGACGATGACACCAAATACG
AGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAAGAAGCCGCTGCTACTGGAGAACGCTT
TTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTGCCAACGACGTCATGGGATCAGCTGAA
TCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGGAGCAGATGTGATCAACCTGAGTCTTGGAACCG
CTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAAAAAGCTAAAAAAGCCGGTGTATC
AGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATGACCCATTGGCAACAAATCCAGAC
TATGGTTTGGTTGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTGGCAGCTATAAACAGTAAGTGGGTGA
TTCAACGTCTAATGACGGTCAAAGAATTGGAAAACCGTGCCGATTTAAACCATGGTAAAGCCATCTaTTCAGA
GTCTGTCGACTTtAAAGACATAAAAGATAGCCTAGGTTATGATAAATCGCATCAATTTGCTTATGTCAAAGAG
TCAACTGATGCGGGTTATAAAGCACAAGACGTTAAAGATAAAATTGCTTTAATTGAACGTGATCCCAATAAAA
CCTATGACGAAATGATTGCTTTGGCTAAGAAACATGGAGCCCTGGGGGTACTTATTTTTAATAACAAGCCTGG
TCAATCAAACCGCTCAATGCGTCTAACAGCTAATGGGATGGGGATACCATCTGCTTTCATATCGCACGAATTT
GGTAAGGCCATGTCCCAATTAAATGGCAATGGTACAGGAAGTTTAGAGTTTGACAGTGTGGTCTCAAAAGCAC
CGAGTCAAAAAGGCAATGAAATGAATCATTTTTCAAATTGGGGCCTAACTTCTGATGGCTATTTAAAACCTGA

CATTACTGCACCAGGCGGCGATATCTACTCTACCTATAACGATAACCACTATGGTAGCCAAACAGGAACAAGT
ATGGCCTCTCCTCAGATTGCTGGCGCCAGCCTTTTGGTCAAACAATATCTAGAAAAGACTCAGCCAAACTTGC
CAAAAGAAAAAATTGCTGATATCGTTAAGAACCTATTGATGAGCAATGCTCAAATTCATGTTAATCCAGAGAC
AAAAACGACCACCTCACCGCGTCAGCAAGGGGCA

> Spy0416A-1 / Schmitz 1/22 (serotype 4); SEQ ID NO: 175
GCAGATGAGCTAACCACAACGAGTGAACCAACAATCACGAATCACGCTCAACAACAAGCGCAACATCTCACCA
ATACAGAGTTGAGCTCAGCTGAATCACAATCCCCAGACACATCACAAATCACTCCCAAGACAAATCGTGAAAA
AGAGCAACCACAAGGTCTAGTCTCTGAGCCAACCACAACTGAGCTAGCTGACACAGATGCAGCATCAATGGCT
AATACAGGTCCTGATGCGACTCAAAAAAGCGCTTCTTTACCGCCAGTCAATACAGATGTTCACGATTGGGTAA
AAACCAAAGGAGCTTGGGACAAGGGATACAAAGGACAAGGCAAGGTTGTCGCAGTTATTGACACAGGGATCGA
TCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAAAATCAAAAGAAGACATGCTAGCA
CGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGTTGTTTTTGCACATAATTATGTGG
AAAATAGCGATAATATCAAAGAAAATCAATTCGGGGATTTTGATGAGGACTGGGAAAACTTTGAGTTTGATGC
AGAGCCAAAAGCCATCAAAAAAAACAAGATCTATCGTCCCCAATCAACCCAGGCACCGAAAGAAACTGTTATC
AAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACAAACAGACGATGACACCAAATACGAGTCAC
ACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAAGAAGCCGCTGCTACTGGAGAACGCTTTTTAGG
AATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTGCCAACGACGTCATGGGATCAGCTGAATCACTC
TTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGGAGCAGATGTGATCAACCTGAGTCTTGGAACCGCTAATG
GGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAAAAAGCTAAAAAAGCCGGTGTATCAGTTGT
TGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATGATCCATTGGCAACAAATCCAGACTATGGT
TTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTGGCAGCTATAAACAGTAAGTGGGTGATTCAAC
GTCTAATGACGGCCAAAGAATTAGAAAACCGTGCCGATTTAAACCATGGTAAAGCCATCTATTCAGAGTCTGT
CGACTTTAAAGACATAAAAGATAGCCTAGGTTATGATAAATCGCATCAATTTGCTTATGTCAAAGAGTCAACT
GATGCGGGTTATAAAGCACAAGACGTTAAAGATAAAATTGCTTTAATTGAACGTGATCCCAATAAAACCTATG
ACGAAATGATTGCTTTGGCTAAGAAACATGGAGCCCTGGGAGTACTTATTTTTAATAACAAGCCTGGTCAATC
AAACCGCTCAATGCGTCTAACAGCTAATGGGATGGGGATACCATCTGCTTTCATATCGCACGAATTTGGTAAG
GCCATGTCCCAATTAAATGGCAATGGTACAGGAAGTTTAGAGTTTGACAGTGTGGTCTCAAAAGCACCGAGTC
AAAAAGGCAATGAAATGAATCATTTTTCAAATTGGGGCCTAACTTCTGATGGCTATTTAAAACCTGACATTAC
TGCACCAGGTGGCGATATCTACTCTACCTATAACGATAACCACTATGGTAGCCAAACAGGAACAAGTATGGCC
TCTCCTCAGATTGCTGGCGCCAGCCTTTTGGTCAAACAATACCTAGAAAAGACTCAGCCAAACTTGCCAAAAG
AAAAAATTGCTGATATCGTTAAGAACCTATTGATGAGCAATGCTCAAATTCATGTTAATCCAGAGACAAAAAC
GACCACCTCACCGCGTCAGCAAGGGGCA

3.4 Antigenic fragment Spy0416A-6

> Spy0416A-6 / SF370 (serotype 1); SEQ ID NO: 15
GCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAA
AATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGT
TGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTTGATGAGGAC
TGGGAAAACTTTGAGTTTGATGCAGAGGCAGAGCCAAAAGCCATCAAAAAAACACAAGATCTATCGTCCCCAAT
CAACCCAGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACA
AACAGACGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAAGAA
GCCGCTGCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTGCCA
ACGACATCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGGAGCAGATGT
GATCAACCTGAGTCTTGGAACCGCTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAA
AAAGCTAAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATG
ATCCATTGGCGACAAATCCAGACTATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTGGC
AGCTATAAACAGTAAGTGGGTGATTCAACGTCTAATGACGGTCAAAGAATTAGAAAACCGTGCCGATTTAAAC
CATGGTAAAGCCATCTATTCAGAGTCTGTCGACTTTAAAGACATAAAAGATAGCCTA

3.5 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0416A-6 / Schmitz 1/7 (serotype 4); SEQ ID NO: 176
GCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAA
AATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGT
TGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGGGGATTTTGATGAGGAC
TGGGAAAACTTTGAGTTTGATGCAGAGCCAAAAGCCATCAAAAAAAACAAGATCTATCGTCCCCAATCAACCC
AGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACAAACAGA
CGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAAGAAGCCGCT

GCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTGCCAACGACG
TCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGGAGCAGATGTGATCAA
CCTGAGTCTTGGAACCGCTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAAAAAGCT
AAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATGATCCAT
TGGCAACAAATCCAGACTATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTGGCAGCTAT
AAACAGTAAGTGGGTGATTCAACGTCTAATGACGGCCAAAGAATTAGAAAACCGTGCCGATTTAAACCATGGT
AAAGCCATCTATTCAGAGTCTGTCGActttaaagacataaaagatagccta

> Spy0416A-6 / Schmitz 1/39 (serotype 12); SEQ ID NO: 177
GCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAA
AATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGT
TGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTTGATGAGGAC
TGGGAAAACTTTGAGTTTGATGCAGAGGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATCGTCCCCAAT
CAACCCAGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACA
AACAGACGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAAGAA
GCCGCTGCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTGCCA
ACGACGTCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGGAGCAGATGT
GATCAACCTGAGTCTTGGAACCGCTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAA
AAAGCTAAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATG
ATCCATTGGCAACAAATCCAGACTATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTGGC
AGCTATAAACAGTAAGTGGGTGATTCAACGTCTAATGACGGTCAAAGAATTAGAAAACCGTGCCGATTTAAAC
CATGGTAAAGCCATCTaTTCAGAGTCTGTCGActttaaaGACATAAAAGATAGCCTA

> Spy0416A-6 / Schmitz 1/55 (serotype 118); SEQ ID NO: 178
GCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAA
AATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGT
TGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTTGATGAGGAC
TGGGAAAACTTTGAGTTTGATGCAGAGGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATCGTCCCCAAT
CAACCCAGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACA
AACAGACGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAAGAA
GCCGCTGCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTGCCA
ACGACGTCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCCTTAGGAGCAGATGT
GATCAACCTGAGTCTTGGAACCGCTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAA
AAAGCTAAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATG
ATCCATTGGCGACAAATCCAGACTATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTAGC
AGCTATAAACAGTAAGTGGGTGATTCAACGTCTAATGACGGTCAAAGAATTGGAAAACCGTGCCGATTTAAAC
CATGGTAAAGCCATCTaTTCAGAGTCTGTCGACTTTAAAGACATAAAAGATAGCCTA

> Spy0416A-6 / Schmitz 1/56 (serotype 28); SEQ ID NO: 179
GCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAA
AATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGT
TGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTTGATGAGGAC
TGGGAAAACTTTGAGTTTGATGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATCGTCCCCAATCAACCC
AGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACAAACAGA
CGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGTAAAGAAGCCGCT
GCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGACCCAAGTCATGTTCATGCGTGTTTTTGCCAACGACG
TCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCCTTAGGAGCAGATGTGATCAA
CCTGAGTCTTGGGACCGCTAATGGTGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAAAAAGCT
AAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATGATCCAT
TGGCAACAAATCCAGACTATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTGGCAGCTAT
AAACAGTAAGTGGGTGATTCAACGTCTAATGACGGTCAAAGAATTAGAAAACCGTGCCGATTTAAACCATGGT
AAAGCCATCTaTTCAGAGTCTGTCGACTTtAAAGACATAAAAGATAGCCTA

> Spy0416A-6 / Schmitz 1/94 (serotype 1); SEQ ID NO: 180
GCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAA
AATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGT
TGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTTGATGAGGAC
TGGGAAAACTTTGAGTTTGATGCAGAGGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATCGTCCCCAAT
CAACCCAGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACA
AACAGACGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAAGAA

GCCGCTGCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTGCCA
ACGACATCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGGAGCAGATGT
GATCAACCTGAGTCTTGGAACCGCTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAA
AAAGCTAAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATG
ATCCATTGGCGACAAATCCAGACTATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTGGC
AGCTATAAACAGTAAGTGGGTGATTCAACGTCTAATGACGGTCAAAGAATTAGAAAACCGTGCCGATTTAAAC
CATGGTAAAGCCATCTATTCAGAGTCTGTCGACTttAAAGACATAAAAGATAGCCTA

> Spy0416A-6 / Schmitz 1/253 (serotype 49); SEQ ID NO: 181
GCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAA
AATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGT
TGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTTGATGAGGAC
TGGGAAAACTTTGAGTTTGATGCAGATGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATCGTCCCCAAT
CAACCCAGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACA
AACAGACGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAAGAA
GCCGCTGCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTGCCA
ACGACGTCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGGAGCAGATGT
GATCAACCTGAGTCTTGGAACCGCTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAA
AAAGCTAAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATG
ATCCATTGGCAACAAATCCAGACTATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTGGC
AGCTATAAACAGTAAGTGGGTGATTCAACGTCTAATGACGGTCAAAGGATTAGAAAACCGTGCCGATTTAaAC
CATGGTAAAGCCATCTATTCAGAGTCTGTCGACTTTAAAGACATAAAAGATAGCCTA

> Spy0416A-6 / Schmitz 1/174 (serotype 6); SEQ ID NO: 182
GCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAA
AATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGT
TGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTTGATGAGGAC
TGGGAAAACTTTGAGTTTGATGCAGAGGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATCGTCCCCAAT
CAACCCAGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACA
AACAGACGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAAGAA
GCCGCTGCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTGCCA
ACGACGTCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGGAGCAGATGT
GATCAACCTGAGTCTTGGAACCGCTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAA
AAAGCTAAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATG
ATCCATTGGCAACAAATCCAGACTATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTGGC
AGCTATAAACAGTAAGTGGGTGATTCAACGTCTAATGACGGTCAAAGAATTAGAAAACCGTGCCGATTTAAAC
CATGGTAAAGCCATCTaTTCAGAGTCTGTCGACTTTAAAaACATAAAAGATAGCCTA

> Spy0416A-6 / Schmitz 1/176 (serotype 83); SEQ ID NO: 183
GCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAA
AATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGT
TGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTTGATGAGGAC
TGGGAAAACTTTGAGTTTGATGCAGAGGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATCGTCCCCAAT
CAACCCAGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACA
AACAGACGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAAGAA
GCCGCTGCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTGCCA
ACGACGTCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGGAGCAGATGT
GATCAACCTGAGTCTTGGAACCGCTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAA
AAAGCTAAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATG
ATCCATTGGCAACAAATCCAGACTATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTGGC
AGCTATAAACAGTAAGTGGGTGATTCAACGTCTAATGACGGTCAAAGAATTAGAAAACCGTGCCGATTTAAAC
CATGGTAAAGCCATCTATTCAGAGTCTGTCGACTTTAAAAACATAAAAGATAGCCTA

> Spy0416A-6 / Schmitz 1/234 (serotype 44); SEQ ID NO: 184
GCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAA
AATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGT
TGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTTGATGAGGAC
TGGGAAAACTTTGAGTTTGATGCAGATGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATCGTCCCCAAT
CAACCCAGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACA
AACAGACGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAAGAA

GCCGCTGCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTGCCA
ACGACGTCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGGAGCAGATGT
GATCAACCTGAGTCTTGGAACCGCTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAA
AAAGCTAAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATG
ACCCATTGGCAACAAATCCAGACTATGGTTTGGTTGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTGGC
AGCTATAAACAGTAAGTGGGTGATTCAACGTCTAATGACGGTCAAAGAATTGGAAAACCGTGCCGATTTAAAC
CATGGTAAAGCCATCTaTTCAGAGTCTGTCGACTTtAAAGACATAAAAGATAGCCTA

> Spy0416A-6 / Schmitz 1/22 (serotype 4); SEQ ID NO: 185
GCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTGCTAAAGTAA
AATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAATGATAAAGT
TGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGGGGATTTTGATGAGGAC
TGGGAAAACTTTGAGTTTGATGCAGAGCCAAAAGCCATCAAAAAAAACAAGATCTATCGTCCCCAATCAACCC
AGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGACACAAACAGA
CGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAAGAAGCCGCT
GCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTGCCAACGACG
TCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGGAGCAGATGTGATCAA
CCTGAGTCTTGGAACCGCTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATTGAAAAAGCT
AAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATGATGATCCAT
TGGCAACAAATCCAGACTATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGTGGCAGCTAT
AAACAGTAAGTGGGTGATTCAACGTCTAATGACGGCCAAAGAATTAGAAAACCGTGCCGATTTAAACCATGGT
AAAGCCATCTATTCAGAGTCTGTCGACTTTAAAGACATAAAAGATAGCCTA

3.6 Antigenic fragment Spy0416A-7

> Spy0416A-7 / SF370 (serotype 1); SEQ ID NO: 16
TCACAAATCACTCTCAAGACAAATCGTGAAAAAGAGCAATCACAAGATCTAGTCTCTGAGCCAACCACAACTG
AGCTAGCTGACACAGATGCAGCATCAATGGCTAATACAGGTTCTGATGCGACTCAAAAAAGCGCTTCTTTACC
GCCAGTCAATACAGATGTTCACGATTGGGTAAAAACCAAAGGAGCTTGGGACAAGGGATACAAAGGACAAGGC
AAGGTTGTCGCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTG
CTAAAGTAAAATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAA
TGATAAAGTTGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTT
GATGAGGACTGGGAAAACTTTGAGTTTGATGCAGAGGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATC
GTCCCCAATCAACCCAGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGA
CTGGACACAAACAGACGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAAT
AGCAAAGAAGCCGCTGCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTG
TTTTTGCCAACGACATCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGG
AGCAGATGTGATCAACCTGAGTCTTGGAACCGCTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAA
GCAATTGAAAAAGCTAAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTG
ACCATGATGATCCATTGGCGACAAATCCAGACTATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAAC
ATCAGTGGCAGCTATAAACAGTAAGTGGGTGATTCAACGTCTAATGACGGTCAAAGAATTAGAAAACCGTGCC
GATTTAAACCATGGTAAAGCCATCTATTCAGAGTCTGTCGACTTTAAAGACATAAAAGATAGCCTAGGTTATG
ATAAATCGCATCAATTTGCTTATGTCAAAGAGTCAACTGATGCGGGTTATAACGCACAAGACGTTAAAGGTAA
AATTGCTTTAATTGAACGTGATCCCAATAAAACCTATGACGAAATGATTGCTTTGGCTAAGAAACATGGAGCT
CTGGGAGTACTTATTTTTAATAACAAGCCTGGTCAATCAAACCGCTCAATGCGTCTAACAGCTAATGGGATGG
GGATACCATCTGCTTTCATATCGCACGAATTTGGTAAGGCCATGTCCCAATTAAATGGCAATGGTACAGGAAG
T

3.7 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0416A-7 / Schmitz 1/7 (serotype 4); SEQ ID NO: 186
TCACAAATCACTCCCAAGACAAATCGTGAAAAAGAGCAACCACAAGGTCTAGTCTCTGAGCCAACCACAACTG
AGCTAGCTGACACAGATGCAGCATCAATGGCTAATACAGGTCCTGATGCGACTCAAAAAAGCGCTTCTTTACC
GCCAGTCAATACAGATGTTCACGATTGGGTAAAAACCAAAGGAGCTTGGGACAAGGGATACAAAGGACAAGGC
AAGGTTGTCGCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTG
CTAAAGTAAAATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAA
TGATAAAGTTGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGGGGATTTT
GATGAGGACTGGGAAAACTTTGAGTTTGATGCAGAGCCAAAAGCCATCAAAAAAAACAAGATCTATCGTCCCC
AATCAACCCAGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGAC
ACAAACAGACGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAA

GAAGCCGCTGCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTG
CCAACGACGTCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGGAGCAGA
TGTGATCAACCTGAGTCTTGGAACCGCTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATT
GAAAAAGCTAAAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATG
ATGATCCATTGGCAACAAATCCAGACTATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGT
GGCAGCTATAAACAGTAAGTGGGTGATTCAACGTCTAATGACGGCCAAAGAATTAGAAAACCGTGCCGATTTA
AACCATGGTAAAGCCATCTATTCAGAGTCTGTCGActttaaagacataaaagatagcctaggttatgataaAT
CGCATCAATTTGCTTATGTCAAaGAGTCAACTGATGCGGGTTATAAAGCACAAGACGTTAAAGATAAAATTGC
TTTAATTGAACGTGATCCCAATAAAACCTATGACGAAATGATTGCTTTGGCTAAGAAACATGGAGCCCTGGGA
GTACTTATTTTTAATAACAAGCCTGGTCAATCAAACCGCTCAATGCGTCTAACAGCTAATGGGATGGGGATAC
CATCTGCTTTCATATCGCACGAATTTGGTAAGGCCATGTCCCAATTAAATGGCAATGGTACAGGAAGT

> Spy0416A-7 / Schmitz 1/39 (serotype 12); SEQ ID NO: 187
TCACAAATCACTCTCAAGACAAATCGTGAAAAAGAGCAACCACAAGGTCTAGTCTCTGAGCCAACCACAACTG
AGCTAGCTGACACAGATGCAGCACCAATGGCTAATACAGGTCCTGATGCGACTCAAAAAAGCGCTTCTTTACC
GCCAGTCAATACAGATGTTCACGATTGGGTAAAAACCAAAGGAGCTTGGGACAAGGGATACAAAGGACAAGGC
AAGGTTGTCGCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTG
CTAAAGTAAAATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAA
TGATAAAGTTGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTT
GATGAGGACTGGGAAAACTTTGAGTTTGATGCAGAGGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATC
GTCCCCAATCAACCCAGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGA
CTGGACACAAACAGACGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAAT
AGCAAAGAAGCCGCTGCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTG
TTTTTGCCAACGACGTCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGG
AGCAGATGTGATCAACCTGAGTCTTGGAACCGCTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAA
GCAATTGAAAAAGCTAAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTG
ACCATGATGATCCATTGGCAACAAATCCAGACTATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAAC
ATCAGTGGCAGCTATAAACAGTAAGTGGGTGATTCAACGTCTAATGACGGTCAAAGAATTAGAAAACCGTGCC
GATTTAAACCATGGTAAAGCCATCTaTTCAGAGTCTGTCGActttaaaGACATAAAAGATAGCCTAGGTTATG
ATAAATCGCATCAATTTGCTTATGTCaAAGAGTCAACTGATGCGGGTTATAACGCACAAGACGTTAAAGGTAA
AATTGCTTTAATTGAACGTGATCCCAATAAAACCTATGACGAAATGATTGCTTTGGCTAAGAAACATGGAGCC
CTGGGAGTACTTATTTTTAATAACAAGCCTGGTCAATCAAACCGCTCAATGCGTCTAACAGCTAATGGGATGG
GGATACCATCTGCTTTCATATCGCACGAATTTGGTAAGGCCATGTCCCAATTAAATGGCAATGGTACAGGAAG
T

> Spy0416A-7 / Schmitz 1/55 (serotype 118); SEQ ID NO: 188
TCACAAGTAACTCCAGAGACAAATCGTGAAAAAGAGCAACCACAAGGTCTAGTCTCTGAGCCAACAACAACTG
AGCTAGCTGACACAGATGCAGCACCAATGGCTAATACAGGTTCTGATGCGACTCAAAAAAGCGCTTCTTTACC
GCCAGTCAATACAGATGTTCACGATTGGGTAAAAACCAAAGGAGCTTGGGACAAGGGATACAAAGGACAAGGC
AAGGTTGTCGCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTG
CTAAAGTAAAATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAA
TGATAAAGTTGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTT
GATGAGGACTGGGAAAACTTTGAGTTTGATGCAGAGGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATC
GTCCCCAATCAACCCAGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGA
CTGGACACAAACAGACGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAAT
AGCAAAGAAGCCGCTGCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTG
TTTTTGCCAACGACGTCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCCTTAGG
AGCAGATGTGATCAACCTGAGTCTTGGAACCGCTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAA
GCAATTGAAAAAGCTAAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTG
ACCATGATGATCCATTGGCGACAAATCCAGACTATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAAC
ATCAGTAGCAGCTATAAACAGTAAGTGGGTGATTCAACGTCTAATGACGGTCAAAGAATTGGAAAACCGTGCC
GATTTAAACCATGGTAAAGCCATCTaTTCAGAGTCTGTCGACTTTAAAGACATAAAAGATAGCCTAGGTTATG
ATAAATCGCATCAATTTGCTTATGTCAaAGAGTCAACTGATGCGGGTTATAACGCACAAAACGTTAAAGGTAA
AATTGCTTTAATTGAACGTGATCCCAATAAAACCTATGACGAAATGATTGCTTTGGCTAAGAAACATGGAGCC
CTGGGAGTACTTATTTTTAATAACAAGCCTGGTCAATCAAACCGCTCAATGCGTCTAACAGCTAATGGGATGG
GGATACCATCTGCTTTCATATCGCACGAATTTGGTAAGGCCATGTCCCAATTAAATGGCAATGGTACAGGAAG
T

> Spy0416A-7 / Schmitz 1/56 (serotype 28); SEQ ID NO: 189
TCACAAATCACTCCCAAGATAAATCGTGAAAAAGAGCAACCACAAGGTCTAGTCTCTGAGCCAACCACAACTG

AGCTAGCTGACACAGATGCAGCACCAATGGCTAATACAGGTCCTGATGCGACTCAAAAAAGCGCTTCTTTACC
GCCAGTCAATACAGATGTTCACGATTGGGTAAAAACCAAAGGAGCTTGGGACAAGGGGTACAAAGGACAAGGT
AAGGTTGTCGCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTG
CTAAAGTAAAATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAA
TGATAAAGTTGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTT
GATGAGGACTGGGAAAACTTTGAGTTTGATGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATCGTCCCC
AATCAACCCAGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGAC
ACAAACAGACGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGTAAA
GAAGCCGCTGCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGACCCAAGTCATGTTCATGCGTGTTTTTG
CCAACGACGTCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCCTTAGGAGCAGA
TGTGATCAACCTGAGTCTTGGGACCGCTAATGGTGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATT
GAAAAAGCTAAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATG
ATGATCCATTGGCAACAAATCCAGACTATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGT
GGCAGCTATAAACAGTAAGTGGGTGATTCAACGTCTAATGACGGTCAAAGAATTAGAAAACCGTGCCGATTTA
AACCATGGTAAAGCCATCTaTTCAGAGTCTGTCGACTTtAAAGACATAAAAGATAGCCTAGGTTATGATAAAT
CGCATCAATTTGCTTATGTCAAAGAGTCAACTGATGCGGGTTATAACGCACAAGACGTTAAAGGTAAAATTGC
TTTAATTGAACGTGATCCCAATAAAACCTATGACGAAATGATTGCTTTGGCTAAGAAACATGGAGCCCTGGGA
GTACTTATTTTTAATAACAAGCCTGGTCAATCAAACCGCTCAATGCGCCTAACAGCTAATGGGATGGGGATAC
CATCTGCTTTCATATCGCACGAATTTGGTAAGGCCATGTCCCAATTAAATGGCAATGGTACAGGAAGT

> Spy0416A-7 / Schmitz 1/94 (serotype 1); SEQ ID NO: 190
TCACAAATCACTCTCAAGACAAATCGTGAAAAAGAGCAATCACAAGATCTAGTCTCTGAGCCAACCACAACTG
AGCTAGCTGACACAGATGCAGCATCAATGGCTAATACAGGTTCTGATGCGACTCAAAAAAGCGCTTCTTTACC
GCCAGTCAATACAGATGTTCACGATTGGGTAAAAACCAAAGGAGCTTGGGACAAGGGATACAAAGGACAAGGC
AAGGTTGTCGCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTG
CTAAAGTAAAATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAA
TGATAAAGTTGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTT
GATGAGGACTGGGAAAACTTTGAGTTTGATGCAGAGGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATC
GTCCCCAATCAACCCAGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGA
CTGGACACAAACAGACGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAAT
AGCAAAGAAGCCGCTGCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTG
TTTTTGCCAACGACATCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGG
AGCAGATGTGATCAACCTGAGTCTTGGAACCGCTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAA
GCAATTGAAAAAGCTAAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTG
ACCATGATGATCCATTGGCGACAAATCCAGACTATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAAC
ATCAGTGGCAGCTATAAACAGTAAGTGGGTGATTCAACGTCTAATGACGGTCAAAGAATTAGAAAACCGTGCC
GATTTAAACCATGGTAAAGCCATCTATTCAGAGTCTGTCGACTttAAAGACATAAAAGATAGCCTAGGTTATG
ATAAATCGCATCAATTTGCTTATGTCaAAGAGTCAACTGATGCGGGTTATAACGCACAAGACGTTAAAGGTAA
AATTGCTTTAATTGAACGTGATCCCAATAAAACCTATGACGAAATGATTGCTTTGGCTAAGAAACATGGAGCT
CTGGGAGTACTTATTTTTAATAACAAGCCTGGTCAATCAAACCGCTCAATGCGTCTAACAGCTAATGGGATGG
GGATACCATCTGCTTTCATATCGCACGAATTTGGTAAGGCCATGTCCCAATTAAATGGCAATGGTACAGGAAG
T

> Spy0416A-7 / Schmitz 1/253 (serotype 49); SEQ ID NO: 191
TCACAAGTAACTCCAGAGACAAATCGTGAAAAAGAGCAACCACAAGGTCTAGTCTCTGAGCCAACAACAACTG
AGCTAGCTGACACAGATGCAGCACCAATGGCTAATACAGGTCCTGATGCGACTCAAAAAAGCGCTTCTTTACC
GCCAGTCAATACAGATGTTCACGATTGGGTAAAAACCAAAGGAGCTTGGGACAAGGGATACAAAGGACAAGGC
AAGGTTGTCGCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTG
CTAAAGTAAAATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAA
TGATAAAGTTGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTT
GATGAGGACTGGGAAAACTTTGAGTTTGATGCAGATGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATC
GTCCCCAATCAACCCAGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGA
CTGGACACAAACAGACGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAAT
AGCAAAGAAGCCGCTGCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTG
TTTTTGCCAACGACGTCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGG
AGCAGATGTGATCAACCTGAGTCTTGGAACCGCTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAA
GCAATTGAAAAAGCTAAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTG
ACCATGATGATCCATTGGCAACAAATCCAGACTATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAAC
ATCAGTGGCAGCTATAAACAGTAAGTGGGTGATTCAACGTCTAATGACGGTCAAAGGATTAGAAAACCGTGCC
GATTTAaACCATGGTAAAGCCATCTATTCAGAGTCTGTCGACTTTAAAGACATAAAAGATAGCCTAGGTTATG

ATAAATCGCATCAATTTGCTTATGTCAAaGAGTCAACTGATGCGGGTTATAACGCACAAGACGTTAAAGGTAA
AATTGCTTTAATTGAACGTGATCCCAATAAAACCTATGACGAAATGATTGCTTTGGCTAAGAAACATGGAGCC
CTGGGACTACTTATTTTTAATAACAAGTCTGGTCAATCAAACCGCTCAATGCGTCTAACAGCTAATGGGATGG
GGATACCATCTGCTTTCATATCGCACGAATTTGGTAAGGCCATGTCCCAATTAAATGGCAATGGTACAGGAAG
T

> Spy0416A-7 / Schmitz 1/174 (serotype 6); SEQ ID NO: 192
TCACAAATCACTCCCAAGACAAATCGTGAAAAAGAGCAATCACAAGATCTAGTCTCTGAGCCAACCACAACTG
AGCTAGCTGACACAGATGCAGCATCAATGGCTAATACAGGTCCTGATGCGACTCAAAAAAGCGCTTCTTTACC
GCCAGTCAATACAGATGTTCACGATTGGGTAAAAACCAAAGGAGCTTGGGACAAGGGATACAAAGGACAAGGC
AAGGTTGTCGCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTG
CTAAAGTAAAATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAA
TGATAAAGTTGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTT
GATGAGGACTGGGAAAACTTTGAGTTTGATGCAGAGGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATC
GTCCCCAATCAACCCAGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGA
CTGGACACAAACAGACGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAAT
AGCAAAGAAGCCGCTGCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTG
TTTTTGCCAACGACGTCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGG
AGCAGATGTGATCAACCTGAGTCTTGGAACCGCTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAA
GCAATTGAAAAAGCTAAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTG
ACCATGATGATCCATTGGCAACAAATCCAGACTATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAAC
ATCAGTGGCAGCTATAAACAGTAAGTGGGTGATTCAACGTCTAATGACGGTCAAAGAATTAGAAAACCGTGCC
GATTTAAACCATGGTAAAGCCATCTaTTCAGAGTCTGTCGACTTTAAAaACATAAAAGATAGCCTAGGTTATG
ATAAATCGCATCAATTTGCTTATGTCAAaGAGTCAACTGATGCGGGTTATAACGCACAAGACGTTAAAGGTAA
AATTGCTTTAATTGAACGTGATCCCAATAAAACCTATGACGAAATGATTGCTTTGGCTAAGAAACATGGAGCC
CTGGGAGTACTTATTTTTAATAACAAACCTGGTCAATCAAACCGCTCAATGCGCCTAACATCTAATGGGATGG
GAATACCATCTGCTTTCATATCGCACGAATTTGGTAAGGCCATGTCCCAATTAAATGGCAATGGTACAGGAAG
T

> Spy0416A-7 / Schmitz 1/176 (serotype 83); SEQ ID NO: 193
TCACAAATCACTCTCAAGACAAATCGTGAAAAAGAGCAACCACAAGGTCTAGTCTCTGAGCCAACCACAACTG
AGCTAGCTGACACAGATGCAGCACCAATGGCTAATACAGGTCCTGATGCGACTCAAAAAAGCGCTTCTTTACC
GCCAGTCAATACAGATGTTCACGATTGGGTAAAAACCAAAGGAGCTTGGGACAAGGGATACAAAGGACAAGGC
AAGGTTGTCGCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTG
CTAAAGTAAAATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAA
TGATAAAGTTGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTT
GATGAGGACTGGGAAAACTTTGAGTTTGATGCAGAGGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATC
GTCCCCAATCAACCCAGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGA
CTGGACACAAACAGACGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAAT
AGCAAAGAAGCCGCTGCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTG
TTTTTGCCAACGACGTCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGG
AGCAGATGTGATCAACCTGAGTCTTGGAACCGCTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAA
GCAATTGAAAAAGCTAAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTG
ACCATGATGATCCATTGGCAACAAATCCAGACTATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAAC
ATCAGTGGCAGCTATAAACAGTAAGTGGGTGATTCAACGTCTAATGACGGTCAAAGAATTAGAAAACCGTGCC
GATTTAAACCATGGTAAAGCCATCTATTCAGAGTCTGTCGACTTTAAAAACATAAAAGATAGCCTAGGTTATG
ATAAATCGCATCAATTTGCTTATGTCAAAGAGTCAACTGATGCGGGTTATAAAGCACAAGACGTTAAAGGTAA
AATTGCTTTAATTGAACGTGATCCCAATAAAACCTATGACGAAATGATTGCTTTGGCTAAGAAACATGGAGCC
CTGGGAGTACTTATTTTTAATAACAAGCCTGGTCAATCAAACCGCTCAATGCGTCTAACAGCTAATGGGATGG
GGATACCATCTGCTTTCATATCGCACGAATTTGGTAAGGCCATGTCCCAATTAAATGGCAATGGTACAGGAAG
T

> Spy0416A-7 / Schmitz 1/234 (serotype 44); SEQ ID NO: 194
TCACAAATCACTCCCAAGACAAATCGTGAAAAAGAGCAATCACAAGATCTAGTCTCTGAGCCAACAACAACTG
AGCTAGCTGACACAGATGCAGCATCAATGGCTAATACAGGTTCTGATGCGACTCAAAAAAGCGCTTCTTTACC
GCCAGTCAATACAGATGTTCACGATTGGGTAAAAACCAAAGGAGCTTGGGACAAGGGATACAAAGGACAAGGC
AAGGTTGTCGCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTG
CTAAAGTAAAATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAA
TGATAAAGTTGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGAGGATTTT
GATGAGGACTGGGAAAACTTTGAGTTTGATGCAGATGCAGAGCCAAAAGCCATCAAAAAACACAAGATCTATC

GTCCCCAATCAACCCAGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGA
CTGGACACAAACAGACGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAAT
AGCAAAGAAGCCGCTGCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTG
TTTTTGCCAACGACGTCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGG
AGCAGATGTGATCAACCTGAGTCTTGGAACCGCTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAA
GCAATTGAAAAAGCTAAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTG
ACCATGATGACCCATTGGCAACAAATCCAGACTATGGTTTGGTTGGTTCTCCCTCAACAGGTCGAACACCAAC
ATCAGTGGCAGCTATAAACAGTAAGTGGGTGATTCAACGTCTAATGACGGTCAAAGAATTGGAAAACCGTGCC
GATTTAAACCATGGTAAAGCCATCTaTTCAGAGTCTGTCGACTTtAAAGACATAAAAGATAGCCTAGGTTATG
ATAAATCGCATCAATTTGCTTATGTCAAAGAGTCAACTGATGCGGGTTATAAAGCACAAGACGTTAAAGATAA
AATTGCTTTAATTGAACGTGATCCCAATAAAACCTATGACGAAATGATTGCTTTGGCTAAGAAACATGGAGCC
CTGGGGGTACTTATTTTTAATAACAAGCCTGGTCAATCAAACCGCTCAATGCGTCTAACAGCTAATGGGATGG
GGATACCATCTGCTTTCATATCGCACGAATTTGGTAAGGCCATGTCCCAATTAAATGGCAATGGTACAGGAAG
T

> Spy0416A-7 / Schmitz 1/22 (serotype 4); SEQ ID NO: 195
TCACAAATCACTCCCAAGACAAATCGTGAAAAAGAGCAACCACAAGGTCTAGTCTCTGAGCCAACCACAACTG
AGCTAGCTGACACAGATGCAGCATCAATGGCTAATACAGGTCCTGATGCGACTCAAAAAAGCGCTTCTTTACC
GCCAGTCAATACAGATGTTCACGATTGGGTAAAAACCAAAGGAGCTTGGGACAAGGGATACAAAGGACAAGGC
AAGGTTGTCGCAGTTATTGACACAGGGATCGATCCGGCCCATCAAAGCATGCGCATCAGTGATGTATCAACTG
CTAAAGTAAAATCAAAAGAAGACATGCTAGCACGCCAAAAAGCCGCCGGTATTAATTATGGGAGTTGGATAAA
TGATAAAGTTGTTTTTGCACATAATTATGTGGAAAATAGCGATAATATCAAAGAAAATCAATTCGGGGATTTT
GATGAGGACTGGGAAAACTTTGAGTTTGATGCAGAGCCAAAAGCCATCAAAAAAAACAAGATCTATCGTCCCC
AATCAACCCAGGCACCGAAAGAAACTGTTATCAAAACAGAAGAAACAGATGGTTCACATGATATTGACTGGAC
ACAAACAGACGATGACACCAAATACGAGTCACACGGTATGCATGTGACAGGTATTGTAGCCGGTAATAGCAAA
GAAGCCGCTGCTACTGGAGAACGCTTTTTAGGAATTGCACCAGAGGCCCAAGTCATGTTCATGCGTGTTTTTG
CCAACGACGTCATGGGATCAGCTGAATCACTCTTTATCAAAGCTATCGAAGATGCCGTGGCTTTAGGAGCAGA
TGTGATCAACCTGAGTCTTGGAACCGCTAATGGGGCACAGCTTAGTGGCAGCAAGCCTCTAATGGAAGCAATT
GAAAAAGCTAAAAAAGCCGGTGTATCAGTTGTTGTAGCAGCAGGAAATGAGCGCGTCTATGGATCTGACCATG
ATGATCCATTGGCAACAAATCCAGACTATGGTTTGGTCGGTTCTCCCTCAACAGGTCGAACACCAACATCAGT
GGCAGCTATAAACAGTAAGTGGGTGATTCAACGTCTAATGACGGCCAAAGAATTAGAAAACCGTGCCGATTTA
AACCATGGTAAAGCCATCTATTCAGAGTCTGTCGACTTTAAAGACATAAAAGATAGCCTAGGTTATGATAAAT
CGCATCAATTTGCTTATGTCAAAGAGTCAACTGATGCGGGTTATAAAGCACAAGACGTTAAAGATAAAATTGC
TTTAATTGAACGTGATCCCAATAAAACCTATGACGAAATGATTGCTTTGGCTAAGAAACATGGAGCCCTGGGA
GTACTTATTTTTAATAACAAGCCTGGTCAATCAAACCGCTCAATGCGTCTAACAGCTAATGGGATGGGGATAC
CATCTGCTTTCATATCGCACGAATTTGGTAAGGCCATGTCCCAATTAAATGGCAATGGTACAGGAAGT

4. Spy0872

4.1 Full length Spy0872

> Spy0872 / SF370 (serotype 1); SEQ ID NO: 196
GATCAAGTTGATGTGCAATTCCTTGGCGTCAATGATTTTCACGGCGCTCTTGATAATACCGGAACAGCTTACA
CACCAAGTGGTAAAATACCAAATGCTGGGACGGCTGCTCAATTAGGTGCTTATATGGATGACGCTGAGATAGA
CTTCAAGCAAGCAAATCAAGACGGAACAAGTATACGTGTTCAAGCTGGAGATATGGTCGGAGCCAGTCCTGCT
AACTCTGCACTTTTACAAGATGAGCCTACTGTCAAAGTCTTTAACAAAATGAAATTTGAATATGGCACTCTTG
GTAATCATGAATTTGACGAAGGACTAGATGAATTTAACCGTATCATGACAGGTCAAGCGCCTGATCCTGAATC
AACAATTAATGATATCACCAAACAATATGAGCACGAAGCTTCGCATCAAACCATCGTCATTGCTAATGTTATT
GATAAAAAAACCAAGGATATCCCCTATGGTTGGAAACCTTATGCTATAAAAGACATAGCCATTAATGACAAAA
TCGTTAAGATTGGCTTCATTGGTGTTGTGACTACAGAGATTCCAAATCTCGTTTTAAAGCAAAACTATGAACA
CTATCAATTTTTAGATGTAGCTGAAACCATTGCCAAATATGCTAAAGAACTACAAGAACAACATGTTCATGCT
ATTGTGGTTTTAGCTCATGTTCCTGCAACAAGTAAAGATGGTGTTGTTGATCATGAAATGGCTACGGTTATGG
AAAAAGTGAACCAAATCTATCCCGAACATAGCATTGATATTATTTTTGCAGGACATAATCATCAATACACTAA
TGGAACTATCGGTAAAACACGTATCGTTCAAGCCCTCTCTCAAGGAAAAGCTTATGCAGATGTCCGTGGTACG
CTAGATACTGATACCAATGATTTTATTAAAACTCCATCAGCAAATGTTGTTGCTGTAGCACCAGGTATCAAAA
CAGAAAATTCAGATATCAAAGCTATAATAAATCATGCTAATGATATTGTTAAAACAGTTACTGAACGAAAAAT
CGGAACTGCAACTAATTCTTCAACTATTTCTAAAACAGAAAATATTGATAAAGAATCTCCTGTCGGTAACTTA
GCAACAACGGCTCAGCTTACTATTGCTAAGAAAACTTTTCCAACTGTTGACTTTGCTATGACCAATAATGGTG
GTATTCGAAGTGACCTAGTTGTCAAAAATGACCGGACCATCACCTGGGGAGCTGCACAGGCTGTACAACCATT
TGGTAATATCCTTCAAGTCATTCAAATGACTGGTCAACACATTTACGATGTCCTAAATCAGCAATACGATGAA

AACCAGACCTATTTTCTTCAAATGTCAGGTTTAACATACACTTATACAGATAATGATCCTAAGAACTCTGATA
CCCCCTTCAAGATAGTTAAGGTTTATAAAGACAATGGTGAAGAAATTAACTTAACAACTACTTACACCGTTGT
TGTCAACGACTTTCTTTATGGTGGTGGTGATGGCTTTTCAGCATTTAAAAAAGCTAAATTAATCGGAGCTATT
AACACAGATACTGAAGCTTTCATCACATATATCACAAATTTAGAAGCATCAGGTAAAACTGTTAATGCTACTA
TAAAAGGGGTTAAAAATTATGTAACTTCAAACCTTGAAAGTTCGACAAAAGTTAATAGTGCTGGTAAACACAG
TATCATTAGTAAGGTTTTTAGAAATCGTGATGGCAATACAGTGTCTAGTGAAGTCATTTCAGACCTTTTGACT
TCTACTGAAAACACTAATAACAGCCTTGGCAAAAAAGAAACAACAACAAACAAAAATACTATCTCTAGTTCCA
CTCTTCCAATAACA

4.2 Antigenic fragment Spy0872-2

> Spy0872-2 / SF370 (serotype 1); SEQ ID NO: 17
GCTATAATAAATCATGCTAATGATATTGTTAAAACAGTTACTGAACGAAAAATCGGAACTGCAACTAATTCTT
CAACTATTTCTAAAACAGAAAATATTGATAAAGAATCTCCTGTCGGTAACTTAGCAACAACGGCTCAGCTTAC
TATTGCTAAGAAAACTTTTCCAACTGTTGACTTTGCTATGACCAATAATGGTGGTATTCGAAGTGACCTAGTT
GTCAAAAATGACCGGACCATCACCTGGGGAGCTGCACAGGCTGTACAACCATTTGGTAATATCCTTCAAGTCA
TTCAAATGACTGGTCAACACATTTACGATGTCCTAAATCAGCAATACGATGAAAACCAGACCTATTTTCTTCA
AATGTCAGGTTTAACATACACTTATACAGATAATGATCCTAAGAACTCTGATACCCCCTTCAAGATAGTTAAG
GTTTATAAAGACAATGGTGAAGAAATTAACTTAACAACTACTTACACCGTTGTTGTCAACGACTTTCTTTATG
GTGGTGGTGATGGCTTTTCAGCATTTAAAAAAGCTAAATTAATCGGAGCTATTAACACAGATACTGAAGCTTT
CATCACATATATCACAAATTTAGAAGCATCAGGTAAAACTGTTAATGCTACTATAAAAGGGGTTAAAAATTAT
GTAACTTCAAACCTTGAAAGTTCGACAAAAGTTAATAGTGCTGGTAAACACAGTATCATTAGTAAGGTTTTTA
GAAATCGTGATGGCAATACAGTGTCTAGTGAAGTCATTTCAGACCTTTTGACTTCTACTGAAAACACTAATAA
CAGCCTTGGCAAAAAAGAAACAACAACAAACAAAAATACTATCTCTAGTTCCACTCTTCCAATAACA

4.3 Homologous sequences of other *S. pyogenes* isolates and/or serotypes

> Spy0872-2 / Schmitz 1/7 (serotype 4); SEQ ID NO: 197
GCTATAATAAATCATGCTAATGATATTGTTAAAACAGTTACTGAACGAAAAATCGGAACTGCAACTAATTCTT
CAACTATTTCTAAAACAGAAAATATTGATAAAGAATCTCCTGTCGGTAACTTAGTAACAACGGCTCAGCTTAC
TATTGCTAAGAAAACTTTTCCAACTGTTGACTTTGCTATGACCAATAATGGTGGTATTCGAAGTGACCTAGTT
GTCAAAAATGACCGGACCATCACCTGGGAAGCTGCACAGGCTGTACAACCATTTGGTAATATCCTTCAAGTCA
TTCAAATGACTGGTCAACACATTTACGATGTCCTAAATCAGCAATACGATGAAAACCAGACCTATTTTCTTCA
AATGTCAGGTTTAACATACACTTATACAGATAATGATCCTAAGAACTCTGATACCCCCTTCAAGATAGTTAAG
GTTTATAAAGACAATGGTGAAGAAATTAACTTAACAACTACTTACACCGTTGTTGTCAACGACTTTCTTTATG
GTGGTGGTGATGGCTTTTCAGCATTTAAAAAAGCTAAATTAATCGGAGCTATTAACACAGATACTGAAGCTTT
CATCACATATATCACAAATTTAGAAGCATCAGGTAAAACTGTTAATGCTACTATAAAAGGGGTTAAAAATTAT
GTAACTTCAAACCTTGAAAGTTCGACAAAAGTTAATAGTGCTGGTAAACACAGTATCATTATCATTAGTAAGG
TTTTTAGAAATCGTGATGGCAATATAGTGTCTAGTGAAATCATTTCAGACCTTTTGACTTCTACTGAAAACAC
TAATAACAGCTTTGGCAAAAAAGAGATAACAACAAAcaAAAATACTATCTCTAATTCCACTCTTCCAATAACA

> Spy0872-2 / Schmitz 1/39 (serotype 12); SEQ ID NO: 198
GCTATAATAAATCATGCTAATGATATTGTTAAAaCAGTTACTGAACGAAAAATCGGAACTGCAACTAATTCTT
CAACTATTTCTAAAACAGAAAATATTGATAAAGAATCTCCTGTCGGTAACTTAGTAACAACGGCTCAGCTTAC
TATTGCTAAGAAAACTTTTCCAACTGTTGACTTTGCTATGACCAATAATGGTGGTATTCGAAGTGACCTAGTT
GTCAAAAATGACCGGACCATCACCTGGGGAGCTGCACAGGCTGTACAACCATTTGGTAATATCCTTCAAGTCA
TTCAAATGACTGGTCAACACATTTACGATGTCCTAAATCAGCAATACGATGAAAACCAGACCTATTTTCTTCA
AATGTCAGGTTTAACATACACTTATACAGATAATGATCCTAAGAACTCTGATACCCCCTTCAAGATAGTTAAG
GTTTATAAAGACAATGGTGAAGAAATTAACTTAACAACTACTTACACCGTTGTTGTCAACGACTTTCTTTATG
GTGGTGGTGATGGCTTTTCAGCATTTAAAAAAGCTAAATTAATCGGAGCTATTAACACAGATACTGAAGCTTT
CATCACATATATCACAAATTTAGAAGCATCAGGTAAAACTGTTAATGCTACTATAAAAGGGGTTAAAAATTAT
GTAACTTCAAACCTTGAAAGCTCGACAAAAGTTAATAGTGCTGGTAAACACAGTATCATTAGTAAGGTTTTTA
GAAATCGTGATGGCAATATAGTGTCTAGTGAAATCATTTCAGACCTTTTGACTTCTACTGAAAACACTAATAA
CAGCCTTGGCAAAAAAGAAACAACGACAAACAAAAATACTATCTCTAGTTCCACTCTTCCAATAACA

> Spy0872-2 / Schmitz 1/55 (serotype 118); SEQ ID NO: 199
GCTATAATAAaTCATGCTAATGATATTGTTAAAACAGTTACTGAACGAAAAATCGGAACTGCAACTAATTCTT
CAACTATTTCTAAAACAGAAAATATTGATAAAGAATCTCCTGTCGGTAACTTAGTAACAACGGCTCAGCTTAC
TATTGCTAAGAAAACTTTTCCAACTGTTGACTTTGCTATGACCAATAATGGTGGTATTCGAAGTGACCTAGTT
GTCAAAAATGACCGGACCATCACCTGGGGAGCTGCACAGGCTGTACAACCATTTGGTAATATCCTTCAAGTCA

TTCAAATGACTGGTCAACACATTTACGATGTCCTAAATCAGCAATACGATGAAAACCAGACCTATTTTCTTCA
AATGTCAGGTTTAACATACACTTATACAGATAATGATCCTAAGAACTCTGATATCCCCTTCAAGATAGTTAAG
GTTTATAAAGACAATGGTGAAGAAATTAACTTAACAACTACTTACACCGTTGTTGTCAACGACTTTCTTTATG
GTGGTGGTGATGGCTTTTCAGCATTTAAAAAAGCTAAATTAATCGGAGCTATTAATACAGATACTGAAGCTTT
CATCACATATATCACAAATTTAGAAGCATCAGGTAAAACTGTTAATGCTACTATAAAAGGGGTTAAAAATTAT
GTAACTTCAAACCTTGAAAGTTCGACAAAAGTTAATAGTGCTGGTAAACACAGTATCATTAGTAAGGTTTTTA
GAAATCGTGATGGCAATATAGTGTCTAGTGAAGTCATTTCAGACCTTTTGACTTCTACTGAAAACACTAATAA
CAGCCTTGGCAAAAAAGAAACAaCGACAAACAAAAATACTATCTCTAGTTCCACTCTTCCAATAACA

> Spy0872-2 / Schmitz 1/56 (serotype 28); SEQ ID NO: 200
GCTATAATAAATCATGCTAATGATATTGTTAAAACAGTTACTGAACGAAAAATCGGAACTGCAACTAATTCTT
CAACTATTTCTAAAACAGAAAATATTGATAAAGAATCTCCTGTCGGTAACTTAGTAACAACAGCTCAGCTTAC
TATTGCTAAGAAAACTTTTCCAACTGTTGACTTTGCTATGACCAATAATGGTGGTATTCGAAGTGACCTAGTT
GTCAAAAATGATCGGACCATCACCTGGGGAGCTGCACAGGCTGTACAACCATTTGGTAATATCCTTCAAGTCA
TTCAAATGACTGGTCAACACATTTACGATGTCCTAAATCAGCAATACGATGAAAACCAGACCTATTTTCTTCA
AATGTCAGGTTTAACATACACTTATACAGATAATGATCCTAAGAACTCTGATACCCCCTTCAAGATAGTTAAG
GTTTATAAAGACAATGGTGAAGAAATTAACTTAACAACTACTTACACCGTTGTTGTCAACGACTTTCTTTATG
GTGGTGGTGATGGCTTTTCAGCATTTAAAAAAGCTAAATTAATTGGAGCTATTAACACAGATACTGAAGCTTT
CATCACATATATCACAAATTTAGAAGCATCAGGTAAAACTGTTAATGCTACTATAAAAGGGGTTAAAAATTAT
GTAACTTCAAACCTTGAAAGTTCGACAAAAGTTAATAGTGCTGGTAAACACAGTATCATTAGTAAGGTTTTTA
GAAATCGTGATGGCAATATAGTGTCTAGTGAGATCATTTCAGACCTTTTGACTTCTACTGAAAACACTAATAA
CAGCCTTGGCAAAAAAGAAACAACAACAAACAAAAATACTATCTCTAGTTCCACTCTTCCAATAACA

> Spy0872-2 / Schmitz 1/94 (serotype 1); SEQ ID NO: 201
GCTATAATAAATCATGCTAATGATATTGTTAAAACAGTTACTGAACGAAAAATCGGAACTGCAACTAATTCTT
CAACTATTTCTAAAACAGAAAATATTGATAAAGAATCTCCTGTCGGTAACTTAGCAACAACGGCTCAGCTTAC
TATTGCTAAGAAAACTTTTCCAACTGTTGACTTTGCTATGACCAATAATGGTGGTATTCGAAGTGACCTAGTT
GTCAAAAATGACCGGACCATCACCTGGGGAGCTGCACAGGCTGTACAACCATTTGGTAATATCCTTCAAGTCA
TTCAAATGACTGGTCAACACATTTACGATGTCCTAAATCAGCAATACGATGAAAACCAGACCTATTTTCTTCA
AATGTCAGGTTTAACATACACTTATACAGATAATGATCCTAAGAACTCTGATACCCCCTTCAAGATAGTTAAG
GTTTATAAAGACAATGGTGAAGAAATTAACTTAACAACTACTTACACCGTTGTTGTCAACGACTTTCTTTATG
GTGGTGGTGATGGCTTTTCAGCATTTAAAAAAGCTAAATTAATCGGAGCTATTAACACAGATACTGAAGCTTT
CATCACATATATCACAAATTTAGAAGCATCAGGTAAAACTGTTAATGCTACTATAAAAGGGGTTAAAAATTAT
GTAACTTCAAACCTTGAAAGTTCGACAAAAGTTAATAGTGCTGGTAAACACAGTATCATTAGTAAGGTTTTTA
GAAATCGTGATGGCAATACAGTGTCTAGTGAAGTCATTTCAGACCTTTTGACTTCTACTGAAAACACTAATAA
CAGCCTTGGCAAAAAAGAAACAACAACAAACAAAAATACTATCTCTAGTTCCACTCTTCCAATAACA

> Spy0872-2 / Schmitz 1/253 (serotype 49); SEQ ID NO: 202
GCTATAATAAATCATGCTAATGATATTGTTAAAaCAGTTACTGAACGAAAAATCGGAACTGCAACTAATTCTT
CAACTATTTCTAAAACAGAAAATATTGATAAAGAATCTCCTGTCGGTAACTTAGTAACAACAGCTCAGCTTAC
TATTGCTAAGAAAACTTTTCCAACTGTTGACTTTGCTATGACCAATAATGGTGGTATTCGAAGTGACCTAGTT
GTCAAAAATGATCGGACCATCACCTGGGGAGCTGCACAGGCTGTACAACCATTTGGTAATATCCTTCAAGTCA
TTCAAATGACTGGTCAACACATTTACGATGTCCTAAATCAGCAATACGATGAAAACCAGACCTATTTTCTTCA
AATGTCAGGTTTAACATTCACTTATACAGATAATGATCCTAAGAACTCTGATACCCCCTTCAAGATAGTTAAG
GTTTATAAAGACAATGGTGAAGAAATTAACTTAACAACTACTTACACCGTTGTTGTCAACGACTTTCTTTATG
GTGGTGGTGATGGCTTTTCAGCATTTAAAAAAGCTAAATTAATTGGAGCTATTAACACAGATACTGAAGCTTT
CATCACATATATCACAAATTTAGAAGCATCAGGTAAAACTGTTAATGCTACTATAAAAGGGGTTAAAAATTAT
GTAACTTCAAACCTTGAAAGCTCGACAAAAGTTAATAGTGCTGGTAAACACAGTATCATTAGTAAGGTTTTTA
GAAATCGTGATGGCAATATAGTGTCTAGTGAAATAATTTCAGACCTTTTGACTTCTACTGAAAACACTAATAA
CAGCCTTGGCAAAAAAGAAACAACGACaAACAAAAATACTATCTCTAGTTCCACTCTTCCAATAACA

> Spy0872-2 / Schmitz 1/176 (serotype 83); SEQ ID NO: 203
GCTATAATAAATCATGCTAATGATATTGTTAAAACAGTTACTGAACGAAAAATCGGAACTGCAACTAATTCTT
CAACTATTTCTAAAACAGAAAATATTGATAAAGAATCCCCTGTCGGTAACTTAGTAACAACGGCTCAGCTTAC
TATTGCTAAGAAAACTTTTCCAACTGTTGACTTTGCTATGACCAATAATGGTGGTATTCGAAGTGACCTAGTT
GTCAAAAATGACCGGACCATCACCTGGGGAGCTGCACAGGCTGTACAACCATTTGGTAATATCCTTCAAGTCA
TTCAAATGACTGGTCAACACATTTACGATGTCCTAAATCAGCAATACGATGAAAACCAGACCTATTTTCTTCA
AATGTCAGGTTTAACATACACTTATACAGATAATGATCCTAAGAACTCTGATACCCCCTTCAAGATAGTTAAG
GTTTATAAAGACAATGGTGAAGAAATTAACTTAACAACTACTTACACCGTTGTTGTCAACGACTTTCTTTATG
GTGGCGGTGATGGCTTTTCAGCATTTAAAAAAGCTAAATTAGTCGGAGCTATTAACACAGATACTGAAGCTTT

CATCACATATATCACAAATTTACAAGCATCAGGTAAAACTGTTAATGCTACTATCAAAGGGGTTAAAAATTAT
GTAACTTCAAACCTTGAAAGATCAACAAAAATTAATAGTGCTGGCAAACACAGTATCATTAGTAAGGTTTTTA
GAAATCGTGATGGCAATATAGTGTCTAGTGAAGTCATTTCAGACCTTTTGACTTCTACTGAAAACACTAATAA
CAGCTTTGGCAAAaAAGAGACAACAACAAACAAAAATACTATCTCTAATTCCACTCTTCCAATAACA

> Spy0872-2 / Schmitz 1/177 (serotype 22); SEQ ID NO: 204
GCTATAATAAATCATGCTAATGATATTGTTAAAACAGTTACTGAACGAAAAATCGGAACTGCAACTAATTCTT
CAACTATTTCTAAAACAGAAAATATTGATAAAGAATCTCCTGTCGGTAACTTAGTAACAACGGCTCAGCTTAC
TATTGCTAAGAAAACTTTTCCAACTGTTGACTTTGCTATGACCAATAATGGTGGTATTCGAAGTGACCTAGTT
GTCAAAAATGACCGGACCATCACCTGGGGAGCTGCACAGGCTGTACAACCATTTGGTAATATCCTTCAAGTCA
TTCAAATGACTGGTCAACACATTTACGATGTCCTAAATCAGCAATACGATGAAAACCAGACCTATTTTCTTCA
AATGTCAGGTTTAACATACACTTATACAGATAATGATCCTAAGAACTCTGATACCCCCTTCAAGATAGTTAAG
GTTTATAAAGACAATGGTGAAGAAATTAACTTAACAACTACTTACACCGTTGTTGTCAACGACTTTCTTTATG
GTGGTGGTGATGGCTTTTCAGCATTTAAAAAAGCTAAATTAATCGGAGCTATTAACACAGATACTGAAGCTTT
CATCACATATATCACAAATTTAGAAGCATCAGGTAAAACTGTTAATGCTACTATAAAAGGGGTTAAAAATTAT
GTAACTTCAAACCTTGAAAGCTCGACAAAAGTTAATAGTGCTGGTAAACACAGTATCATTAGTAAGGTTTTTA
GAAATCGTGATGGCAATATAGTGTCTAGTGAAATCATTTCAGACCTTTTGACTTCTACTGAAAACACTAATAA
CAGCCTTGGCAAAAAAGAAACaACGACAAACAAAAATACTATCTCTAGTTCCACTCTTCCAATAACA

> Spy0872-2 / Schmitz 1/234 (serotype 44); SEQ ID NO: 205
GCTATAATAAATCATGCTAATGATATTGTTAAAACAGTTACTGAACGAAAAATCGGAACTGCAACTAATTCTT
CAACTATTTCTAAAACAGAAAATATTGATAAAGAATCTCCTGTCGGTAACTTAGTAACAACGGCTCAGCTTAC
TATTGCTAAGAAAACTTTTCCAACTGTTGACTTTGCTATGACCAATAATGGTGGTATTCGAAGTGACCTAGTT
GTCAAAAATGACCGGACCATCACCTGGGGAGCTGCACAGGCTGTACAACCATTTGGTAATATCCTTCAAGTCA
TTCAAATGACTGGTCAACACATTTACGATGTCCTAAATCAGCAATACGATGAAAACCAGACCTATTTTCTTCA
AATGTCAGGTTTAACATACACTTATACAGATAATGATCCTAAGAACTCTGATACCCCCTTCAAGATAGTTAAG
GTTTATAAAGACAATGGTGAAGAAATTAACTTAACAACTACTTACACCGTTGTTGTCAACGACTTTCTTTATG
GTGGTGGTGATGGCTTTTCAGCATTTAAAAAAACTAAATTAATCGGAGCTATTAACACAGATACTGAAGCTTT
CATCACATATATCACAAATTTAGAAGCATCAGGTAAAACTGTTAATGCTACTATAAAAGGGGTTAAAAATTAT
GTAACTTCAAACCTTGAAAGCTCGACAAAAGTTAATAGTGCTGGTAAACACAGTATCATTAGTAAGGTTTTTA
GAAATCGTGATGGCAATATAGTGTCTAGTGAAATCATTTCAGACCTTTTGACTTCTACTGAAAACACTAATAA
CAGCCTTGGCAAAAAAGAAACAACGACaAACAAAAATACTATCTCTAGTTCCACTCTTCCAATAACA

> Spy0872-2 / Schmitz 1/22 (serotype 4); SEQ ID NO: 206
GCTATAATAAATCATGCTAATGATATTGTTAAAACAGTTACTGAACGAAAAATCGGAACTGCAACTAATTCTT
CAACTATTTCTAAAACAGAAAATATTGATAAAGAATCTCCTGTCGGTAACTTAGTAACAACGGCTCAGCTTAC
TATTGCTAAGAAAACTTTTCCAACTGTTGACTTTGCTATGACCAATAATGGTGGTATTCGAAGTGACCTAGTT
GTCAAAAATGACCGGACCATCACCTGGGAAGCTGCACAGGCTGTACAACCATTTGGTAATATCCTTCAAGTCA
TTCAAATGACTGGTCAACACATTTACGATGTCCTAAATCAGCAATACGATGAAAACCAGACCTATTTTCTTCA
AATGTCAGGTTTAACATACACTTATACAGATAATGATCCTAAGAACTCTGATACCCCCTTCAAGATAGTTAAG
GTTTATAAAGACAATGGTGAAGAAATTAACTTAACAACTACTTACACCGTTGTTGTCAACGACTTTCTTTATG
GTGGTGGTGATGGCTTTTCAGCATTTAAAAAAGCTAAATTAATCGGAGCTATTAACACAGATACTGAAGCTTT
CATCACATATATCACAAATTTAGAAGCATCAGGTAAAACTGTTAATGCTACTATAAAAGGGGTTAAAAATTAT
GTAACTTCAAACCTTGAAAGTTCGACAAAAGTTAATAGTGCTGGTAAACACAGTATCATTATCATTAGTAAGG
TTTTTAGAAATCGTGATGGCAATATAGTGTCTAGTGAAATCATTTCAGACCTTTTGACTTCTACTGAAAACAC
TAATAACAGCTTTGGCAAAAAAGAGATAACAACAAACAAAAATACTATCTCTAATTCCACTCTTCCAATAACA

5. Further Sequences

> Spy0488 / SF370 (serotype 1); SEQ ID NO: 18
TTGCGGCAGATTCAGTCCATTCGTCTGATAGACGTTTTGGAGTTGGCTTTTGGAGTTGGCTATAAGGAAGAAA
CAACCTCTCAGTTTTCTTCGGATCAGCCCTCCCAAGTGGTTTTGTATCGAGGTGAGGCTAACACGGTTAGGTT
TGCCTATACCAATCAGATGTCTCTGATGAAAGATATTCGCATTGCTTTGGATGGTTCTGATAAGTCTTTGACC
GCTCAGATTGTTCCTGGTATGGGTCATGTTTATGAGGGCTTTCAAACTTCTGCTAGAGGGATTTTTACGATGT
CAGGAGTTCCTGAAAGCACTGTTCCCGTTGCTAACCCTAATGTACAAACCAAATATATAAGGTATTTCAAAGT
CATTGATGATATGCATAACACAATGTATAAAGGAACTGTTTTTCTTGTTCAACCGCAAGCTTGGAAATACACC
ATGAAATCTGTTGATCAGTTACCAGTAGATGACTTGAACCATATTGGCGTTGCTGGTATTGAACGAATGACAA
CTCTCATTAAAAATGCGGGTGCCCTTTTAACCACAGGAGGTAGTGGGGCTTTCCCAGACAATATTAAAGTATC
TATTAATCCAAAGGGGAGGCAGGCCACGATTACTTATGGGGACGGCTCTACGGATATTATTCCTCCAGCAGTT
TTATGGAAAAAAGGCTCCGTAAAAGAGCCTACTGAAGCCGATCAATCTGTCGGAACACCGACTCCTGGTATTC

CTGGTAAATTCAAACGAGACCAGAGCCTTAACGAGCATGAAGCTATGGTAAATGTCGAACCACTGTCTCATGT
AGTAAAAGACAATATAAAGGTCATAGATGAAAAATCAACAGGGCGGTTTGAGCCTTTTAGACCTAATGAAGAT
GAGAAGGAGAAGCCTGCCAGCGATGTTAAGGTAAGACCAGCAGAAGTTGGTAGCTGGCTAGAACCAGCGACAG
CTCTTCCTAGTGTTGAAATGAGCGCTGAGGACAGGTTAAAAAGT

> Spy0895 / SF370 (serotype 1); SEQ ID NO: 19
ACTAATAATCAAACACTAGACATCCTTTTGGATGTCTATGCTTATAATCACGCCTTTAGAATTGCTAAAGCCT
TGCCAAATATCCCTAAAACTGCCCTCTATTTACTAGAGATGTTAAAAGAGCGCAGAGAATTGAACCTTGCCTT
TCTAGCGGAACATGCAGCAGAGAATCGGACCATTGAAGACCAGTATCACTGTTCATTATGGCTTAACCAATCG
CTTGAAGATGAGCAGATTGCCAATTACATTTTGGATTTAGAAGTTAAAGTAAAAAACGGTGCTATTATTGATT
TCGTCAGGTCAGTGTCGCCTATTCTTTACCGACTTTTTCTCAGACTAATCACGTCAGAAATTCCAAACTTCAA
GGCTTATATTTTTGATACAAAGAATGACCAATATGATACCTGGCATTTTCAGGCCATGTTGGAATCTGATCAC
GAGGTTTTCAAGGCTTACCTGTCTCAAAAGCAGTCTCGCAATGTGACGACCAAAAGCTTAGCAGACATGTTGA
CGTTGACCTCCTTACCTCAGGAAATCAAGGACTTGGTTTTTTTGTTACGACATTTTGAAAAGGCTGTCCGTAA
TCCTCTGGCTCATTTGATTAAGCCTTTTGATGAAGAGGAACTGCATCGCACCACTCATTTTTCTTCTCAGGCT
TTTTTGGAAAACATTATCACCTTGGCGACTTTTTCTGGTGTAATCTACCGACGTGAGCCTTTTTACTTTGATG
ACATGAATGCCATTATTAAAAAGGAGTTGAGCCTTTGGAGACAATCTATTGTC

> Spy1536 / SF370 (serotype 1); SEQ ID NO: 207
ATTGAAATGCCTGGAGGCGCTTACGATATTCGGACTGTCTTACAAGTCAATGGCAAAGAAGACAAACGAAAAG
GAGCTTACCAGTTTGTTGCAGTGGGCATTAGTCGTGCCAGCCTCGCTCAGCTATTATATGCTTGGCTGACACC
GTTTACTGAAATTAGTACAGCAGAAGATACAACAGGCGGATACAGCGATGCTGATTTCCTTCGAATTAATCAA
TTTTACATGGAAACATCACAAAATGCAGCTATTTATCAAGCTTTATCCTTAGCTGGAAAACCAGTTACATTAG
ATTATAAAGGCGTATATGTTTTAGACGTAAACAACGAATCTACTTTTAAAGGAACGCTACACTTAGCAGATAC
TGTAACAGGTGTAAATGGTAAACAGTTTACTAGTTCAGCAGAACTTATTGACTATGTTTCTCACCTAAAACTA
GGGGATGAAGTTACGGTTCAGTTTACGAGTGATAATAAGCCTAAAAAAGGAGTTGGCCGTATTATCAAACTGA
AAAATGGGAAAAATGGGATTGGCATTGCCTTGACTGATCATACAAGTGTCAATTCAGAAGACACAGTGATCTT
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GTGGTGCAGGTCTTAAAGTAGTTGCAGCAGCTGAAGCTGGTGCAGATATATTTTTTGTTCCGAATAATCCTGT
TGATAAGGAAATTAAAAAAGTTAATCCAAATGCTATAAGTAATTACGAAGAAGCCAAACGGGCAGCCAAACGA
CTAAAGACCAAAATGAAGATTGTTCCTGTTACGACTGTTCAAGAGGCACTGGTTTATCTTCGCAAA

> Spy1666 / SF370 (serotype 1); SEQ ID NO: 208
ACAAAAGAATTTCATCACGTGACCGTACTCCTTCACGAAACAGTGGACATGCTTGACATAAAGCCTGATGGGA
TTTATGTTGATGCGACGCTAGGTGGCTCAGGCCACTCAGCTTATTTGTTGTCCAAACTTGGTGAAGAAGGGCA
CCTCTATTGTTTTGACCAAGACCAAAAGGCTATTGACAATGCACAAGTTACCCTCAAATCTTATATTGACAAA
GGACAGGTAACTTTTATTAAAGATAATTTTAGACACCTCAAAGCACGTTTAACAGCGCTTGGAGTTGATGAAA
TTGATGGTATCTTATATGACCTTGGTGTTTCCAGCCCGCAATTGGATGAAAGAGAACGAGGGTTTTCTTATAA
ACAAGATGCTCCATTGGATATGCGCATGGATCGTCAGTCGCTCTTAACAGCTTACGAAGTGGTGAATACCTAT
CCATTCAATGATTTGGTTAAGATTTTTTTCAAATATGGTGAAGATAAATTCTCCAAGCAGATCGCTCGAAAAA
TTGAACAAGCAAGAGCTATTAAGCCTATTGAGACAACAACAGAGTTGGCAGAATTGATTAAGGCAGCAAAGCC
AGCTAAAGAGTTGAAGAAAAAAGGCCACCCTGCTAAACAGATTTTTCAAGCTATTCGCATTGAAGTCAATGAT
GAATTGGGAGCGGCCGATGAATCTATTCAGGACGCTATGGAATTATTAGCCCTTGATGGTCGTATCTCAGTTA
TTACCTTCCATTCTCTGGAAGATCGCCTAACCAAGCAGTTGTTTAAAGAAGCTAGTACGGTGGATGTGCCAAA
AGGGCTTCCTCTAATTCCTGAAGATATGAAACCTAAGTTTGAACTTGTTTCACGTAAGCCGATCTTACCTAGT
CATTCAGAGTTAACAGCTAATAAAAGGGCACACTCAGCCAAGCTACGTGTTGCCAAAAAAATTCGGAAA

> Spy1727 / SF370 (serotype 1); SEQ ID NO: 20
GTGACAACGACGGAACAAGAACTTACCTTGACTCCCTTACGTGGGAAAAGTGGCAAAGCTTATAAAGGCACTT
ATCCAAATGGGGAATGTGTCTTTATAAAATTAAATACGACCCCTATTCTACCTGCCTTAGCAAAAGAACAGAT
TGCGCCACAGTTACTTTGGGCCAAACGCATGGGCAATGGTGATATGATGAGTGCCCAAGAATGGCTTAACGGC
CGTACATTGACCAAAGAAGATATGAACAGTAAGCAAATCATTCATATTCTATTGCGCCTTCACAAATCTAAAA
AATTAGTCAATCAACTGCTTCAGCTCAATTATAAGATTGAAAACCCATACGATTTATTGGTTGATTTTGAGCA
AAATGCACCCTTGCAAATTCAGCAAAATTCATACTTACAAGCTATCGTTAAAGAATTAAAACGGAGCTTACCA
GAGTTCAAATCAGAAGTAGCAACGATTGTGCATGGAGATATTAAACATAGCAATTGGGTGATTACTACTAGTG
GTATGATTTTTTTAGTAGATTGGGATTCTGTTCGTCTAACTGATCGGATGTATGATGTTGCTTACCTGTTGAG
CCACTATATTCCACGGTCTCGTTGGTCAGAATGGCTGTCTTATTATGGCTATAAAAATAATGACAAGGTTATG
CAAAAAATTATTTGGTATGGTCAATTTTCTCACCTGACACAAATTCTCAAGTGTTTTGACAAGCGTGACATGG
AGCATGTGAATCAGGAGATTTATGCCCTCAGAAAATTTAGAGAAATATTTAGAAAGAAA

Claims

1. A peptide consisting of one antigen of *S. pyogenes* of the SEQ ID NO: 4, SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 7, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 3 or a functional active variant of one antigen of *S. pyogenes* of the SEQ ID NO: 4, SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 7, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 3.

2. A peptide consisting of one antigen of *S. pyogenes* of the SEQ ID NO: 4, SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 7, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 3 or a functional active variant of one antigen of *S. pyogenes* of the SEQ ID NO: 4, SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 7, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 3, and

   a) 1 to 350 additional amino acid residue(s), preferably 1 to 200, more preferably 1 to 150, even more preferably at most 1 to 100, still more preferably at most 1 to 50, most preferably 1, 2, 3, 4, 5, 10, 15, 20 or 25 additional amino acids residue(s) if the antigen is SEQ ID NO: 1; or

   b) 1 to 200 additional amino acid residue(s), preferably 1 to 150, more preferably 1 to 100, even more preferably at most 1 to 50, still more preferably at most 1 to 25, most preferably 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 additional amino acids residue(s) if the antigen is SEQ ID NO: 2; or

   c) 1 to 100 additional amino acid residue(s), preferably 1 to 75, more preferably 1 to 50, even more preferably at most 1 to 25, still more preferably at most 1 to 10, most preferably 1, 2, 3, 4 or 5 additional amino acids residue(s) if the antigen is that of SEQ ID NO: 3; or

   d) 1 to 150 additional amino acid residue(s), preferably 1 to 100, more preferably 1 to 75, even more preferably at most 1 to 50, still more preferably at most 1 to 25, most preferably 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 additional amino acids residue(s) if the antigen is that of SEQ ID NO: 4; or

   e) 1 to 450 additional amino acid residue(s), preferably 1 to 300, more preferably 1 to 150, even more preferably at most 1 to 100, still more

preferably at most 1 to 50, most preferably 1, 2, 3, 4, 5, 10, 20, 30 or 40 additional amino acids residue(s) if the antigen is SEQ ID NO: 5; or

f) 1 to 250 additional amino acid residue(s), preferably 1 to 200, more preferably 1 to 150, even more preferably at most 1 to 100, still more preferably at most 1 to 50, most preferably 1, 2, 3, 4, 5, 10, 15, 20 or 25 additional amino acids residue(s) if the antigen is SEQ ID NO: 6 or SEQ ID NO: 7.

3. The peptide of any of claims 1 or 2 further consisting of at least one amino acid residue heterologous to the antigen, preferably an additional amino acid sequence comprising a marker protein.

4. The peptide of any of claims 2 or 3, wherein the additional amino acid residue(s) is/are flanking the antigen C-terminally, N-terminally or C- and N-terminally.

5. The peptide of any of claims 1 to 4, wherein the functional active variant is essentially identical to any of the antigens of the SEQ ID NO: 4, SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 7, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 3, but differs from the antigens of any of the SEQ ID NO: 4, SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 7, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 3 in that it is derived from a homologous sequence of a different serotype of *S. pyogenes*, particularly wherein the serotype is M2, M3, M4, M5, M6, M11, M12, M14, M19, M22, M24, M25, M28, M44, M49, M57, M59, M60, M61, M76, M83, M84, M87, M89 or M118.

6. The peptide of any of claims 1 to 5, wherein the functional active variant is a portion of any of the SEQ ID NOS: 1 to 7 consisting of at least 60%, preferably at least 70%, more preferably at least 80%, still more preferably at least 90%, even more preferably at least 95%, most preferably 99% of the amino acids of the antigen of any of the SEQ ID NOS: 1 to 7.

7. The peptide of any of claims 1 to 6, wherein the functional active variant of the antigen of any of the SEQ ID NOS: 1 to 7 has at least 50% sequence identity to the

antigen of any of the SEQ ID NOS: 1 to 7, especially at least 60%, preferably at least 70%, more preferably at least 80%, still more preferably at least 90%, even more preferably at least 95%, most preferably 99% sequence identity to the antigen of any of the SEQ ID NOS: 1 to 7.

8. The peptide of claim 7, wherein the variant is derived from the antigen of any of the SEQ ID NOS: 1 to 7 by at least one conservative amino acid substitution.

9. A peptide comprising an amino acid sequence with at least 95% sequence identity to at least one of SEQ ID NO: 1, 2, 3, 4, 5, 6 or 7, wherein said peptide is not Spy0269, Spy0292, Spy0416A, or Spy0872.

10. A peptide characterized in that it comprises at least 2, preferably at least 3, more preferably at least 4 antigens as defined in any of claims 1 to 9.

11. A nucleic acid coding for the peptide according to any of claims 1 to 10 or a nucleic acid complementary thereto, particularly a DNA sequence of any of the sequences of SEQ ID NOS: 11 to 17 or the corresponding RNA sequence.

12. The nucleic acid of claim 11, wherein the nucleic acid is located in a vector.

13. A pharmaceutical composition, especially a vaccine, comprising
(i) at least one peptide according to any of claims 1 to 10 and/or
(ii) at least one peptide comprising or consisting of the sequence of any of the SEQ ID NO: 8, SEQ ID NO: 9, or SEQ ID NO: 10, or a functional active variant thereof, and
(iii) optionally a pharmaceutically acceptable carrier or excipient.

14. A pharmaceutical composition containing
(i) a nucleic acid according to claim 11 and/or a nucleic acid complementary thereto and/or
(ii) a nucleic acid coding for the peptide comprising or consisting of the sequence of any of the SEQ ID NO: 8, SEQ ID NO: 9, or SEQ ID NO: 10,

particularly a DNA sequence of any of the SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 20, or a functional active variant thereof or a nucleic acid complementary thereto or the corresponding RNA sequence, and

(iii) optionally a pharmaceutically acceptable carrier or excipient.

15. The pharmaceutical composition of claim 14, wherein the nucleic acid is comprised in a vector and/or a cell.

16. An antibody or functional active fragment thereof which binds specifically to the antigen of claim 1.

17. The antibody or functional active fragment thereof of claim 16, wherein the antibody is a monoclonal, polyclonal, chimeric or humanized antibody, or wherein the functional active fragment comprises a Fab fragment.

18. A hybridoma cell line which produces the antibody according to claim 16 or 17.

19. A method for producing an antibody according to claim 16 or 17, characterized by the following steps:

(a) administering an effective amount of the peptide according to any of claims 1 to 10 to an animal; and

(b) isolating the antibody produced by the animal in response to the administration of step (a) from the animal.

20. A method for producing an antibody according to claim 16 or 17, characterized by the following steps:

(a) contacting a B cell with an effective amount of the peptide according to any of claims 1 to 10;

(b) fusing the B cell of step (a) with a myeloma cell to obtain a hybridoma cell; and

(c) isolating the antibody produced by the cultivated hybridoma cell.

21. The method of claim 19 or 20, wherein the isolated antibody is additionally purified.

22. A pharmaceutical composition, especially a vaccine, comprising the antibody according to claim 16 or 17.

23. A pharmaceutical composition comprising the peptide as defined in claim 13 or the nucleic acid as defined in claim 14 or the antibody or functional fragment thereof according to claim 16 or 17 for the immunization of a subject against an infection or the treatment of a subject having an infection, wherein the infection is preferably a *S. pyogenes* infection.

24. Use of the peptide as defined in claim 13 or the nucleic acid as defined in claim 14 or the antibody or functional fragment thereof according to claim 16 or 17 for the manufacture of a medicament for immunization against or treatment of an infection, preferably a *S. pyogenes* infection.

25. Method of immunizing a subject against an infection or treating a subject having an infection, the method comprising

(a) administering to the patient an effective amount of the peptide as defined in claim 13 or the nucleic acid as defined in claim 14 or the antibody or functional fragment thereof according to claim 16 or 17.

26. The method of claim 25, wherein the infection is a *S. pyogenes* infection.

27. A method of diagnosing a *S. pyogenes* infection comprising the steps of:

(a) contacting a sample obtained from a subject with the peptide according to any of claims 1 to 10; and

(b) detecting the presence of an antibody against *S. pyogenes* in the sample.

28. A method of diagnosing a *S. pyogenes* infection comprising the steps of:

(a) contacting a sample obtained from a subject with the antibody according to claim 16 or 17; and

(b) detecting the presence of an antigen of *S. pyogenes* in the sample.

29. A method for identifying a ligand capable of binding to a peptide according to any of claims 1 to 10 comprising:

(a) providing a test system comprising the peptide,

(b) contacting the test system with a test compound, and

(c) detecting a signal generated in response to the binding of the test compound to the peptide or functional active variant.

30. Use of any of the peptide according to any of claims 1 to 10 for the isolation and/or purification and/or identification of an interaction partner of the peptide.

Figure 1 CFA/IFA model

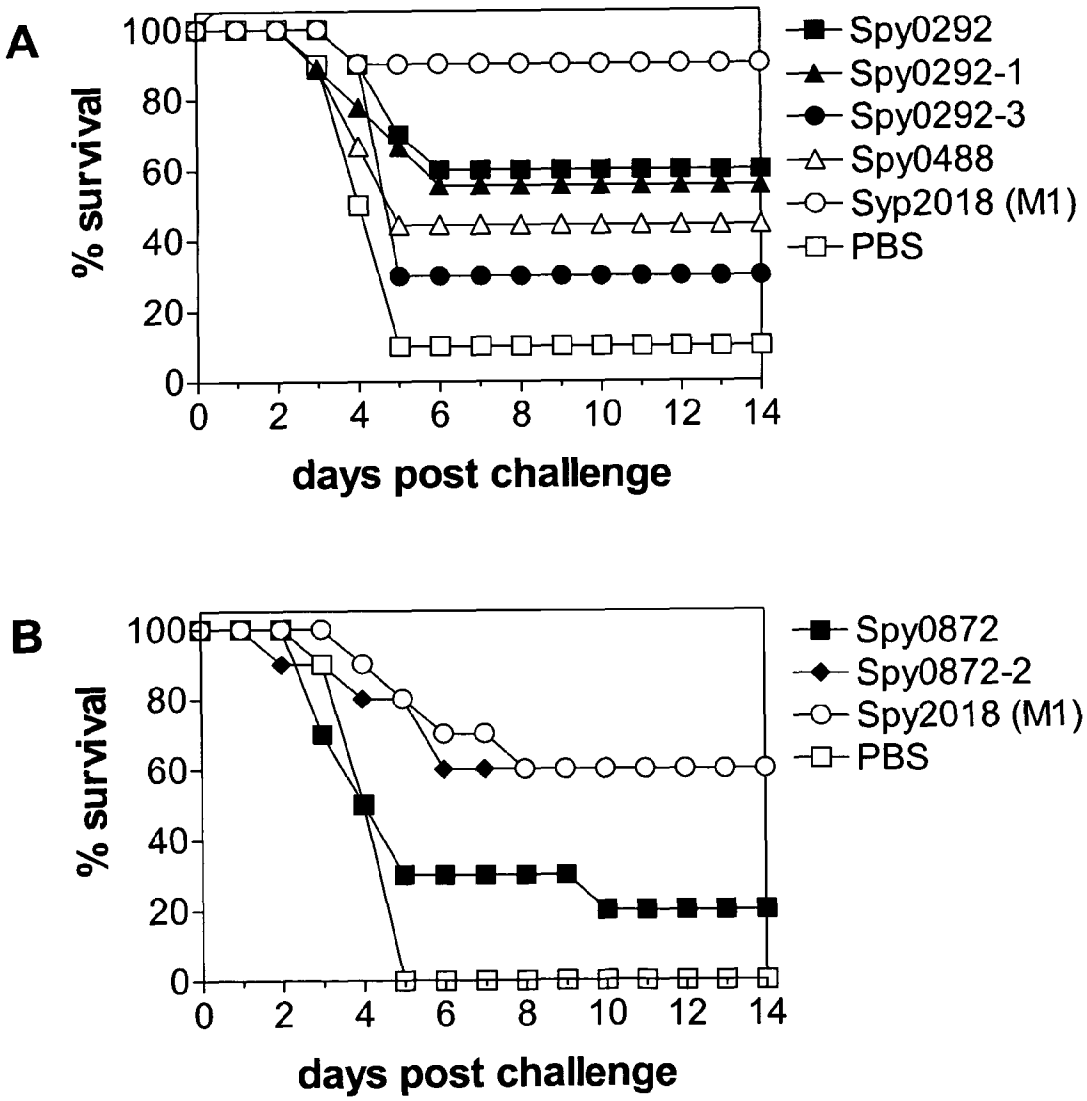


Figure 2 CFA/IFA model

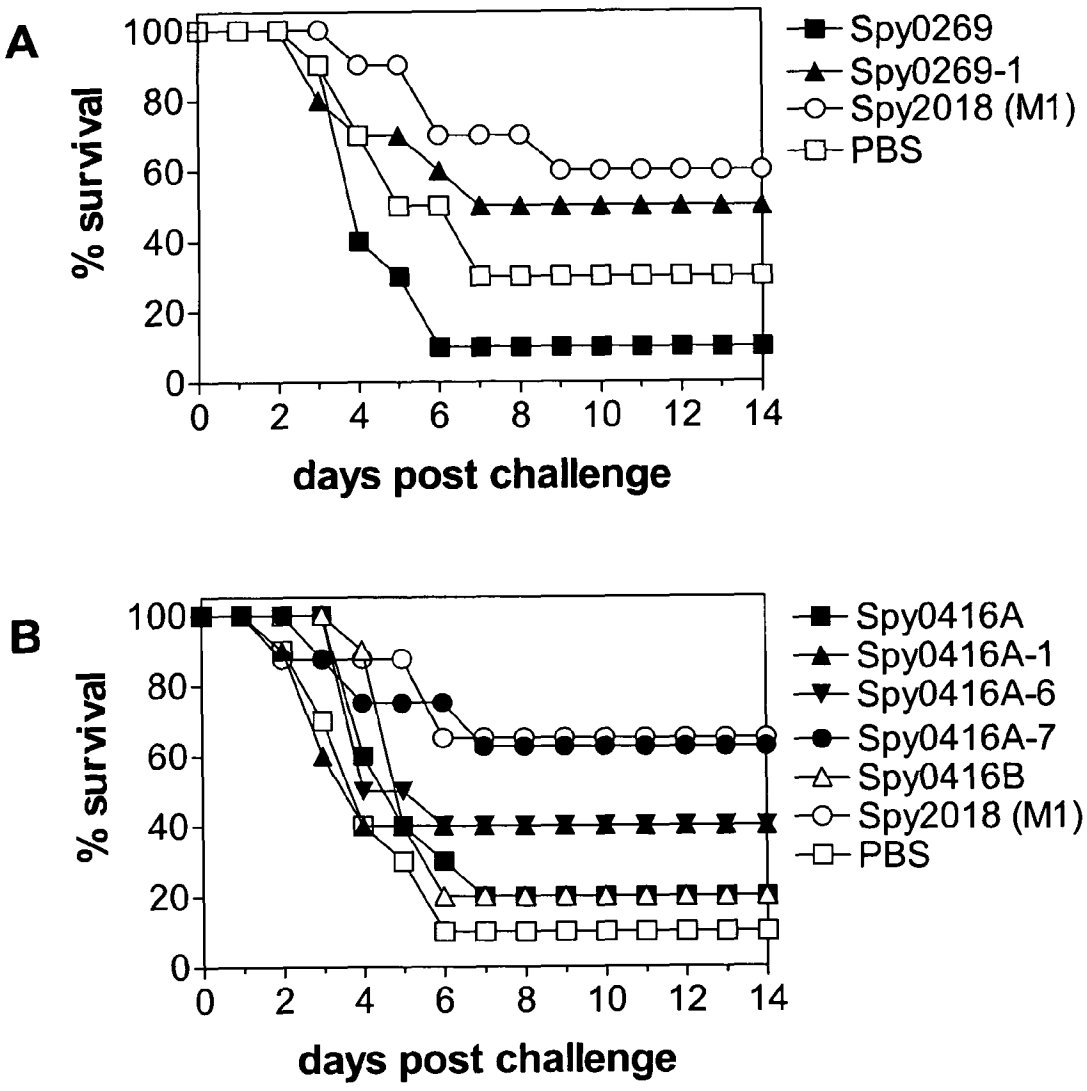


Figure 3 ALUM model

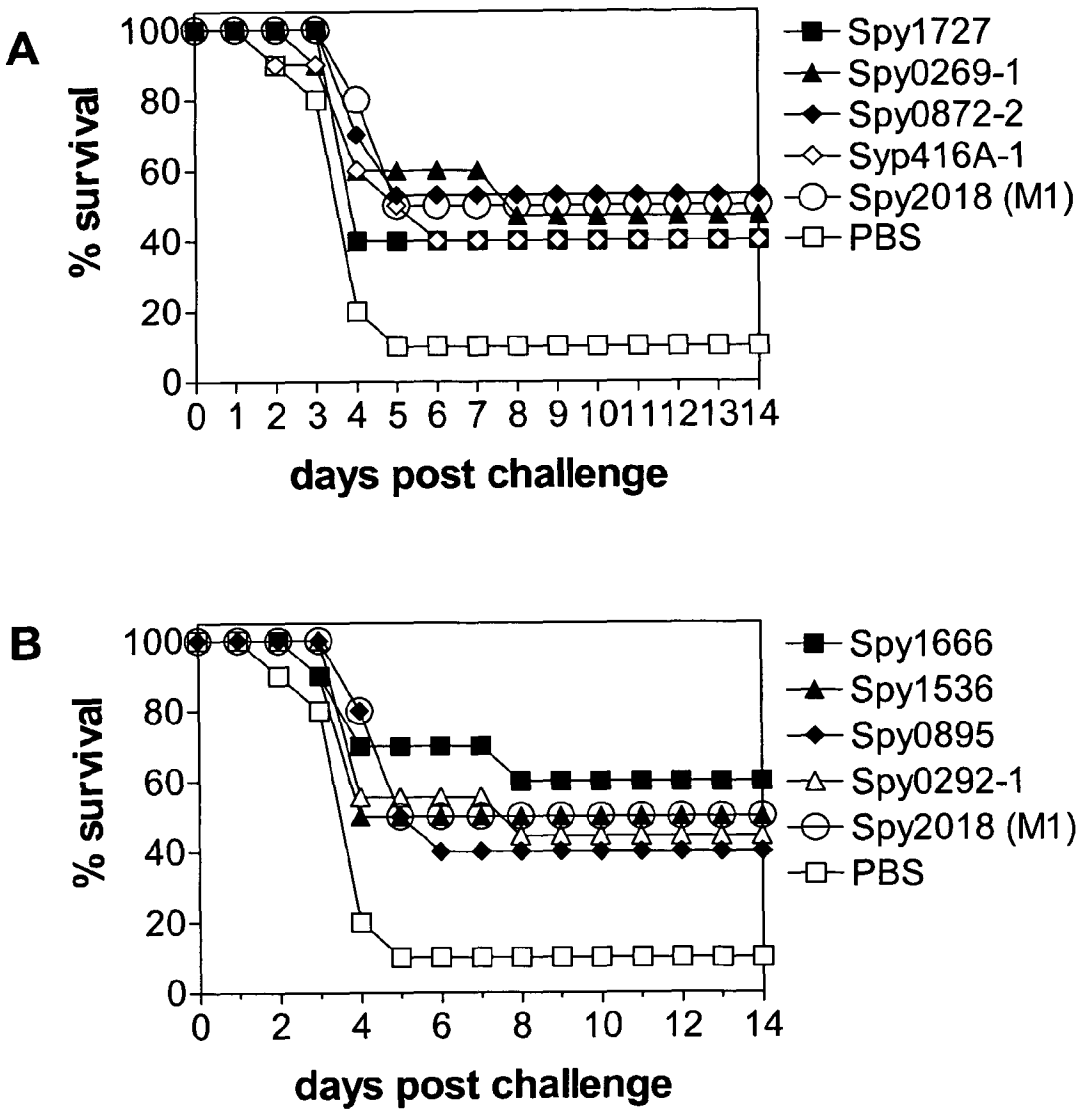
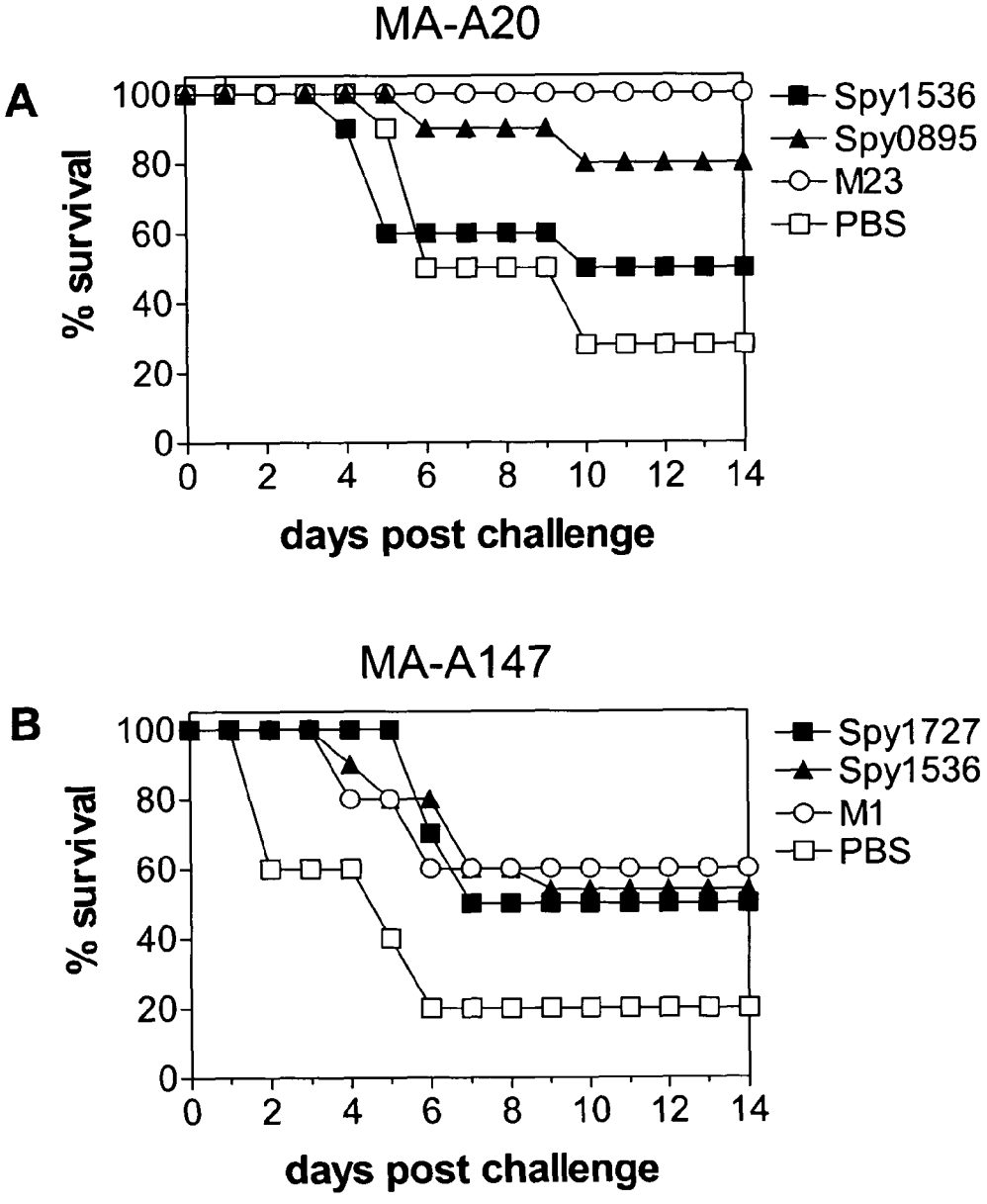


Figure 4 IC31 i.n. model



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/006027

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/032582 A2 (CHIRON CORP [US]; GRANDI GUIDO [US]; TELFORD JOHN [US]; BENSI GIULIANO) 14 April 2005 (2005-04-14) page 26, line 23 - page 53, line 25; claims 2,11,27; sequence 122	1-30

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 September 2007	27/11/2007

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/006027

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-30 (only partially)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 25-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
Although claims 27-28 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-30 (only partially)

   A peptide consisting of SEQ ID NO. 4, or a variant thereof, the nucleic acid encoding it and the uses thereof.

   ---

2. claims: 1-30 (only partially)

   A peptide consisting of SEQ ID NO. 1, or a variant thereof, the nucleic acid encoding it and the uses thereof.

   ---

3. claims: 1-30 (only partially)

   A peptide consisting of SEQ ID NO. 2, or a variant thereof, the nucleic acid encoding it and the uses thereof.

   ---

4. claims: 1-30 (only partially)

   A peptide consisting of SEQ ID NO. 7, or a variant thereof, the nucleic acid encoding it and the uses thereof.

   ---

5. claims: 1-30 (only partially)

   A peptide consisting of SEQ ID NO. 5, or a variant thereof, the nucleic acid encoding it and the uses thereof.

   ---

6. claims: 1-30 (only partially)

   A peptide consisting of SEQ ID NO. 6, or a variant thereof, the nucleic acid encoding it and the uses thereof.

   ---

7. claims: 1-30 (only partially)

   A peptide consisting of SEQ ID NO. 3, or a variant thereof, the nucleic acid encoding it and the uses thereof.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/006027

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005032582 A2	14-04-2005	CA 2532369 A1	14-04-2005
		EP 1648500 A2	26-04-2006
		JP 2007500726 T	18-01-2007